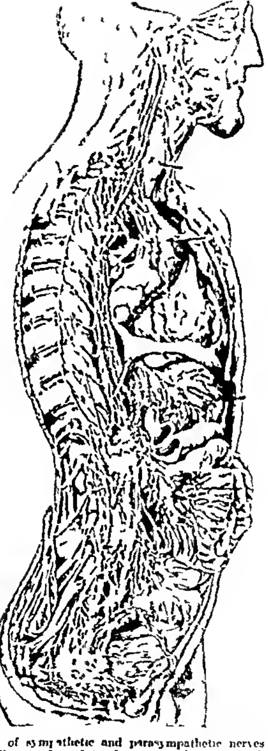

FIG 1 —Distribution of sympathetic and parasympathetic nerves The sympathetic nerves and ganglia are illustrated in white the vagus and parasympathetic nerves in dotted lines and the mixed terminal nerves in darker shade (Modified from Müller)

THE AUTONOMIC NERVOUS SYSTEM

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PREFACE TO THE THIRD EDITION

Knowledge of the anatomy and physiology of the autonomic nervous system and its relation to health and disease has been materially advanced, since the publication of the second edition of this book, by the findings of many investigators. The results obtained in experimental and clinical studies during the past decade are particularly significant since in many instances they amplify the results of earlier anatomic and physiologic studies and thus provide a more adequate basis for the interpretation of the normal functional activity of the autonomic nerves and their modified activity in the presence of disease. Knowledge of the structural and functional relationships of the central autonomic centers, particularly those in the hypothalamus, and the central conduction pathways associated with the latter has been greatly increased. The influence of impulses of cortical origin in the regulation of visceral functions also has been more completely demonstrated. New data obtained in histopathologic studies of autonomic ganglia and nerves have been reported but the histopathologic data available do not afford an adequate basis for the interpretation of all the variations observed in terms of modified function.

In the preparation of the present volume an attempt has been made, on the basis of the results of both the early and the more recent studies, to describe the autonomic nervous system briefly but adequately as a component part of the nervous system as a whole and in relation to the effector organs innervated through the autonomic nerves, to point out its developmental and general physiologic relationships to the cerebrospinal nervous system and to give an account of the more important histopathologic and clinical data bearing on the functional activity of this division of the nervous system in disease.

Adequate consideration of all the anatomic, physiologic, histopathologic and clinical data bearing directly or indirectly on the autonomic nervous system within the limits of a single volume would be impossible. It is extremely difficult, furthermore, to present all the significant findings in their true historical setting. The temptation to give the most recent and best illustrated contributions undue weight is ever present. This tends to create the impression that the latest and most detailed work is the most significant, whereas in reality the later findings have been made possible in a large measure by the original discoveries of earlier investigators. The author desires to give due credit to the pioneer investigators, but space has not been adequate to set forth the complete historical background of our present knowledge regarding many phases of this important subject. Some significant data have been omitted and some have been

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The Autonomic Nervous System

HISTORICAL INTRODUCTION

The vital physiological functions of the body in all the higher animals including man are subject to nervous regulation in some degree. This involves mainly reflex reactions of varying degrees of complexity which are carried out through afferent and efferent conduction systems and reflex and coordinating centers. Peripheral reflex mechanisms have been demonstrated, but the chief reflex and coordinating centers involved in the regulatory control of the visceral functions are located in the central nervous system. The functional activities of these nervous mechanisms are essentially involuntary but not independent of regulatory influences emanating from the cerebral cortex. All the neurons involved in the innervation of the visceral organs which are located outside the central nervous system, except those which are afferent components of the cerebrospinal nerves, are included in the so-called autonomic nervous system. This system also includes the neurons located within the spinal cord and brain stem through which the outlying efferent neurons are functionally connected with the central nervous system.

The earliest anatomical description of any part of the autonomic nervous system probably is Galen's account of a nerve trunk lying along the necks of the ribs which receives fibers from the thoracic and lumbar portions of the spinal cord and gives off branches to the viscera. Galen regarded this nerve as a branch of the vagus and advanced the hypothesis that through it the viscera receive sensitivity from the brain and motor power from the spinal cord. He obviously did not differentiate the cervical portion of the sympathetic trunk from the vagus. He observed three enlargements or ganglia, along the course of the nerve: the first just above the larynx, the second at the entrance of the nerve into the thorax and the third at its entrance into the abdomen. The upper enlargement described by Galen undoubtedly includes the nodose and the superior cervical sympathetic ganglia. The one at the upper border of the thorax obviously is the inferior cervical or cervicothoracic ganglion. The description of the one at the entrance of the nerve into the abdomen probably refers to the semilunar ganglion of the celiac plexus.

Galen also advanced the first widely accepted theory of "sympathy" or "consent" between different parts of the body. He rejected the teaching of Aristotle that the brain serves to cool the blood and attributed to it the function of generating "animal" spirits from the "vital" spirits in the blood. The peripheral nerves were regarded as tubular structures through which the animal spirits are distributed. It was further assumed that wherever peripheral nerves join one another communications are effected through which animal spirits may flow freely from one part of the body to another and thus bring about "sympathy" between various parts of the body.

Galen's description of the vagi, which he regarded as the sixth pair of cranial nerves, was scrupulously followed by all the early anatomists including Vesalius, consequently the gangliated sympathetic trunk and the vagus nerve were regarded as a unit both anatomically and physiologically. The sympathetic trunk probably was first differentiated from the vagus nerve anatomically by Estienne (1545). Eustachio (1552) also recognized the sympathetic trunk as anatomically distinct from the vagus nerve. He later illustrated it as arising within the cranium from the abducens nerve, thus emphasizing its supposedly cerebral origin. This error was not corrected until the publication of du Petit's work in 1727.

Willis (1664) called the gangliated sympathetic trunk the "intercostal" nerve, a name which persisted until the time of Winslow. He also introduced the physiological concept of involuntary as distinct from voluntary movements but erroneously attributed the initiation of involuntary movements to the cerebellum. His account of a branch of the vagus nerve given off to the arch of the aorta undoubtedly is the earliest reference to the depressor nerve. Willis advanced the hypothesis that this nerve reacts to changes in the pulse. He also recognized the vagus innervation of the heart as an important factor in its functional regulation but discovered no specific reaction to vagus stimulation. The observations of Lower (1669) on the effects of vagus section and vagus stimulation on the heart beat, which were later amplified by Ens (1715), prepared the way for the final establishment of the inhibitory action of the vagus nerve on the heart beat by the experimental studies of Weber and Weber (1846).

The physiological concept of involuntary and voluntary movements introduced by Willis was greatly extended by Whytt (1751). His interpretation of involuntary movements on the basis of local stimulation marks the beginning of a new era in physiologic thought and investigation, since it afforded a secure basis for the theory of reflex action. He envisioned reactions like the peristaltic movements of the gastro-intestinal tract and contractions of the urinary bladder as responses of the musculature to nerve stimulation due to local irritation of the mucous membrane or stretching of the muscle fibers due to distention of the organs. The idea of reflex action was thus introduced in the absence of any knowledge of reflex conduction pathways. Whytt's application of this principle to explain the responses of the pupil to light constitutes the earliest known record of the light accommodation and consensual reflexes. He later (1765) advanced the opinion that all "sympathy" or "consent" presupposes feeling and consequently must be mediated through the nerves but not by the flow of any substance through anastomosing channels, since in many instances the sympathy occurs between parts of the body whose nerves effect no connections with one another. Sympathy, therefore, must be referred to the brain and spinal cord which are the source of all nerves. Although he probably had no adequate conception of nerve conduction, he drew attention to nerve fibers as functional units in contradistinction to the older concepts of anastomosing channels.

The erroneous conception of the origin of the "intercostal" nerve from the brain was corrected by du Petit (1727) who pointed out, on the basis of careful dissections and the results of experimental section of the vagosympathetic trunk in dogs, that this nerve is not directly connected with the brain. Although the significance of this work was not fully appreciated

until the time of Gaskell and Langley, investigators following du Petit recognized that the communicating rami constitute the only pathway from the central nervous system to the sympathetic ganglia

Winslow (1732) accepted du Petit's findings, but regarded the sympathetic ganglia as independent nerve centers He discarded the term "intercostal" nerves, which had been commonly applied to the sympathetic trunks, and called them the "great sympathetic" nerves, in accordance with his opinion that they are concerned primarily with the "sympathies" between various organs

Johnstone (1764) advanced the hypothesis that the sympathetic ganglia represent mechanisms through which the movements of the heart and intestine are rendered involuntary, since they intercept the "determinations of the will" and prevent them from reaching certain parts of the body He also advanced the opinion that the ganglia interrupt sensory impressions from the viscera which accounts for the relative lack of sensitivity in the visceral organs His descriptive accounts of the ganglia in relation to the nerves led to the use of the terms "ganglionic nerves" and "ganglionic nervous system" He supported Winslow's view of the relative independence of the ganglia and thus contributed to the propagation of this concept

Meckel (1751) advanced the opinion that the ganglia serve to divide nerves into many fibers, to arrange these fibers according to their course and termination and to reunite them in bundles as they emerge from the ganglia He observed that the volume of the fibers emerging from a ganglion is greater than the volume of those which enter it, but apparently did not surmise that fibers arise within the ganglia

The anatomical and physiological studies of Bichat (1800, 1801, 1802) contributed significantly to knowledge of the autonomic nervous system and stimulated further research He conceived of life as made up of animal life (la vie animale) and organic life (la vie organique), a distinction which finds expression in the current concepts of "somatic" and "visceral" functions He correlated the ganglionic nervous system with metabolic functions and pointed out the continuity of action apparent in the organic life in contrast to the intermittent activity apparent in the animal life In pursuance of this point of view, he regarded the sympathetic ganglia as nerve centers entirely independent of the central nervous system He noted the difference in the appearance of the white and gray communicating rami and regarded the former as components of the central nervous system but failed clearly to recognize their true significance He also observed that the fibers which emerge from the sympathetic ganglia enter the organs mainly along the courses of their arteries Although Bichat commonly used the term, ganglionic nervous system, he may properly be regarded as the originator of the name, "organic nervous system" because of his emphasis on the relation of the ganglionic nerves to organic life

Reil (1807) introduced the term "vegetative nervous system" Like Bichat, he regarded the sympathetic ganglia as independent nerve centers He interpreted the communicating rami as connections between the animal and vegetative nervous systems which serve as semiconductors According to his view, sensory impressions from the viscera do not ordinarily reach the brain, but in disease sensory impressions from the vegetative sphere may be transmitted through the communicating rami and

thus reach the level of consciousness, a view which is strikingly reminiscent of the one advanced by *Johnstone nearly half a century earlier*

The earliest description of nerve cell bodies in sympathetic ganglia probably is that of Ehrenberg (1833), who also recorded some observations on the microscopic structure of nerve fibers Valentin (1836) described the histologic structure of sympathetic ganglia including the ganglion cells, in greater detail He recognized the fibers of the white communicating rami as arising in the spinal cord and entering the sympathetic ganglia, and distinguished between fibers which terminate in the ganglia and those which pass through them, but failed to recognize the nervous nature of the unmyelinated fibers which Remak (1838) described as arising from the sympathetic ganglion cells and which he called "organic" fibers

Bidder and Volkmann (1842) also opposed Remak's view of the "organic" fibers The nervous nature of these fibers gradually became established as Remak's observations were confirmed by other investigators In 1854 Remak published a more extensive account of the structure of the sympathetic ganglia and their connections, particularly the communicating rami Although Beck (1846) had observed that the sympathetic ganglia are connected with the cervical and sacral nerves only through gray communicating rami, Remak maintained that all the spinal nerves possess both white and gray communicating rami In spite of this error, Remak's account afforded the basis for a better understanding of the functional significance of the communicating rami

At the middle of the nineteenth century the relationships of the vagus nerves to the "ganglionic" or "organic" nervous system remained obscure although a vagus influence on cardiac activity had been demonstrated The ciliary, sphenopalatine, otic and submaxillary ganglia were regarded as components of the ganglionic nervous system but their relationships also remained uncertain The submucous plexus in the intestine was described by Meissner in 1857 and the myenteric plexus by Auerbach in 1864 The significant anatomical and physiological studies leading up to Claude Bernard's (1852) discovery of the vasomotor function of the sympathetic nerves to the blood vessels which was confirmed by Brown-Sequard *(1852), had already been accomplished*

The early studies of the vasomotor nerves gave rise to the concept of a universal vasoconstrictor action of sympathetic nerve fibers Vasodilator effects of nerve stimulation were not reported until Bernard (1858) observed dilatation of the arteries supplying the submaxillary gland on stimulation of the chorda tympani Dastre and Morat (1880) later demonstrated the existence of vasodilator fibers in the cervical portion of the sympathetic trunk

In the light of advancing knowledge of the nature of the communicating rami, reflex activity and reflex centers in the central nervous system, Bichat's theory, according to which the sympathetic ganglia represent nerve centers which function independently of the central nervous system could no longer be supported On the basis of extensive physiological data Bernard advanced the hypothesis that all sympathetic reflexes are mediated through the spinal cord He also demonstrated the existence of centers in the brain stem which on stimulation discharge impulses which are conducted peripheralward through sympathetic nerves The search for higher centers which exert their influence through the autonomic nerves was thus initiated

The early anatomical and physiological studies of Gaskell (1886) contributed greatly to a better understanding of the autonomic nervous system His account of the white communicating rami and their distribution represents the earliest account of these nerves which is based on adequate anatomical and histological observations He pointed out that the efferent fibers in these rami arise in the spinal cord in cell columns which are interrupted by the development of the nerves to the limbs He also pointed out the occurrence of corresponding fibers in certain of the cranial nerves and that there exist three outflows of medullated nerve fibers of small caliber, the bulbar, thoracolumbar and sacral, through which the peripherally located efferent ganglion cells are connected with the central nervous system Gaskell classified the ganglia in question as (1) proximal or vertebral and (2) distal The former category included only the ganglia of the sympathetic trunks from the lower cervical segments downward, the latter included (a) the prevertebral ganglia, *i e*, the superior cervical, celiac and superior mesenteric and (2) the terminal ganglia, *i e*, those located within the visceral organs or in proximity to them

In his later work Gaskell (1916) used the term "involuntary nervous system" to designate the efferent neurons located outside the central nervous system which supply fibers to involuntary structures He conceived of the involuntary nervous system as purely motor or efferent and referred to the outflows from the central nervous system as the "connectors" His terminology presented certain obvious difficulties and has never been widely used

Langley and Dickinson (1889) discovered in the action of nicotine on the ganglia a new method of investigating the relationships of nerve fibers to peripheral ganglion cells The results obtained by the use of this method led Langley (1898) to propose a new terminology for the system of nerves in question He called it the "autonomic nervous system," although he was not unmindful of its anatomic and functional relationships to the cerebrospinal nervous system

When the term "autonomic" was introduced by Langley, it was well known that the thoracolumbar outflow through the sympathetic trunks supplies fibers to all parts of the body The cranial and sacral outflows on the other hand were known to supply fibers only to parts of the body It was also known that the functional effects of the thoracolumbar outflow, in general are the opposite of those of the cranial and sacral outflows Langley, therefore, regarded the thoracolumbar outflow as a system distinct from the rest of the autonomic nerves He regarded the part of the cranial outflow supplying the eye as distinct from the bulbar part of this outflow, which with the sacral outflow constitutes a system which innervates the alimentary canal and parts developmentally connected with it On this basis he (1898) divided the autonomic system into tectal bulbosacral and sympathetic systems Following the discovery that the effects produced by adrenin apparently are similar to those produced by stimulation of sympathetic nerves and that certain other drugs produce effects apparently identical with those produced by stimulation of the tectal and bulbosacral nerves, he (1905) grouped the tectal and bulbosacral autonomic nerves together as the parasympathetic system Langley (1900) had previously pointed out that the neurons in the myenteric and submucous plexuses might conceivably be postganglionic neurons in bulbar and sacral efferent

chains, but, since the data available afforded no clear proof of the central connections of these cells and histological evidence had convinced him that they differ structurally from other peripheral neurons, he placed the myenteric and submucous plexuses in a separate system which he called the enteric nervous system. In 1912 he wrote: "This classification is, I think, still advisable, for the central connection of the enteric nerve cells is still uncertain, and evidence has been obtained that they have autonomic and reflex functions which other peripheral nerve cells do not possess."

Langley regarded the autonomic neurons as essentially motor. The autonomic nerves, as he defined them, therefore, were regarded as purely efferent. The afferent nerves accompanying the latter are not in all cases distinguishable from other afferent nerves; consequently, they were not regarded as autonomic.

Although Langley's classification of the nerves in question cannot be regarded as final and he himself recognized the inadequacy of the terminology which he proposed, it is the most satisfactory terminology in use at the present time. Accordingly, the terms autonomic, sympathetic and parasympathetic will be used in the present volume in the sense in which Langley used them. Such minor deviations from Langley's classification and terminology as are introduced will be discussed in their proper connections.

CHAPTER I

MORPHOLOGY AND DISTRIBUTION OF THE AUTONOMIC NERVOUS SYSTEM

Definition and Terminology.—The visceral organs, including the vascular and glandular systems, receive their efferent innervation through the autonomic nervous system. This system, which is neither anatomically separate from the central nervous system nor functionally independent of it, includes all neurons located outside the central nervous system and the cerebrospinal ganglia except the peripheral afferent neurons associated with the special sense organs. It also includes the efferent neurons located within the spinal cord and brain stem through which the outlying autonomic neurons are functionally connected with the central nervous system. With certain exceptions the autonomic neurons outside the central nervous system are arranged in aggregates known as ganglia, the autonomic ganglia. Some of these ganglia are located along the anterolateral aspects of the vertebral column. Those on either side are interconnected by nerve fibers. These series of ganglia, with the interganglionic fibers, constitute the paired sympathetic trunks. Other autonomic ganglia are incorporated in nerve plexuses located in proximity to the thoracic, abdominal and pelvic viscera or within their walls. Still others are located in the cephalic region in relation to certain of the cranial nerves.

The neurons through which the autonomic ganglia are anatomically and functionally connected with the central nervous system are visceral efferent components of the cerebrospinal nerves. They are commonly known as preganglionic neurons. The cell bodies of these neurons are located in the intermediolateral cell column in the spinal cord and the visceral efferent nuclei in the brain stem. Their axons traverse the corresponding spinal and cranial nerves and effect synaptic connections with ganglion cells in the autonomic ganglia. The axons of the autonomic ganglion cells extend peripheralward either in visceral or somatic nerves and terminate in relation to the tissue elements which are innervated through the autonomic nerves.

The afferent neurons through which visceral impulses are conducted into the central nervous system are the general visceral afferent components of the cerebrospinal nerves. The cell bodies of these neurons, like those of the general somatic afferent neurons, are located in the cerebrospinal ganglia. Their peripheral processes traverse the autonomic ganglia without interruption and are not known to effect direct functional connections with peripheral autonomic neurons. Both visceral and somatic afferent neurons effect reflex connections with preganglionic visceral efferent neurons and, consequently, are functionally related to the autonomic nerves. Afferent neurons which terminate in the central nervous system may not be regarded as constituents of the autonomic nerves, however, since both somatic and visceral afferents also effect reflex connections with somatic efferent neurons. They are properly classified as somatic and visceral afferent components, respectively, of the cerebrospinal nerves.

The autonomic reflex arcs with central connections in the central nervous system differ anatomically from the cerebrospinal reflex arcs mainly in that the preganglionic efferent components of the former effect synaptic connections with ganglion cells in the autonomic ganglia, whereas the efferent components of the latter terminate in direct relation to effector organs (Fig 2) The efferent limb of the autonomic reflex arc consequently, comprises two neurons whereas that of the cerebrospinal reflex arc comprises but one The portion of either the autonomic or the cerebrospinal reflex arc which is located within the central nervous system may be confined to a single segment or involve two or more segments The preganglionic component of the autonomic reflex arc likewise may effect synaptic connections in one or more autonomic ganglia

The afferent components of the cerebrospinal nerves which effect reflex connections with preganglionic neurons probably do not terminate in direct relation to these neurons but effect synaptic connections with intercalated neurons which in turn effect synaptic connections with the pre-

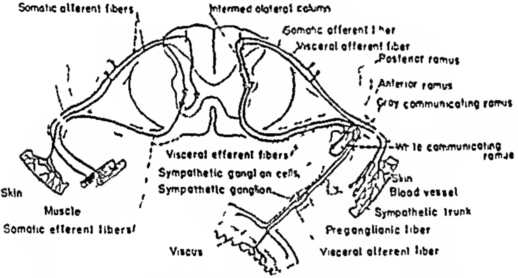

FIG 2 —Diagrammatic illustration of visceral (right) and somatic (left) reflex arcs

ganglionic neurons (Foerster, Gagel and Sheehan, 1933) The preganglionic component of an autonomic reflex arc, consequently, may not be regarded as comparable to the intercalated neuron in the cerebrospinal reflex arc

The distribution of the preganglionic visceral efferent neurons is limited to certain regions of the spinal cord and brain stem Some of the cerebrospinal nerves, consequently, include no visceral efferent components On the basis of the distribution of preganglionic visceral efferent nerve components, the autonomic nervous system may be divided into (1) the cranial division, the preganglionic components of which emerge in the third, seventh, ninth, tenth and eleventh cranial nerves (2) the thoracolumbar division, the preganglionic components of which emerge in the thoracic and upper lumbar nerves, and (3) the sacral division, the preganglionic components of which emerge in the second, third and fourth sacral nerves (Fig 3)

The preganglionic components of the thoracic and upper lumbar nerves traverse the visceral rami of these nerves and join the sympathetic trunk Some of them terminate in the sympathetic trunk ganglia, others traverse these ganglia without effecting connections in them and extend, via the splanchnic nerves, to ganglia located in closer proximity to the abdominal and pelvic viscera The preganglionic components of the cranial and sacral nerves do not traverse the sympathetic trunk but extend through rami of the respective nerves to the ganglia in which they terminate The

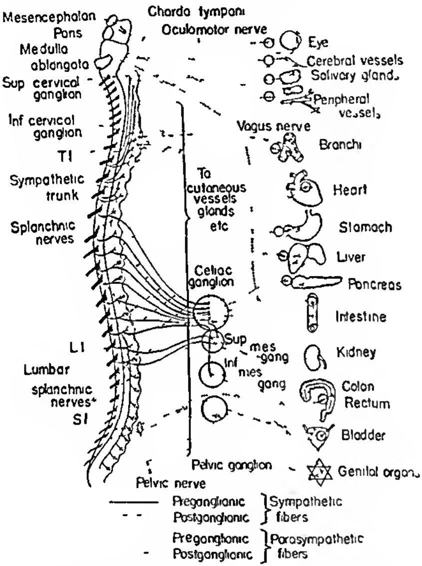

FIG 3 —*Diagrammatic illustration of the distribution of sympathetic and parasympathetic nerves*

cranial and sacral divisions of the autonomic nervous system also react to certain drugs according to the same mode, but differ in this respect from the thoracolumbar division On the basis of the anatomical relationships of their preganglionic components and their pharmacological peculiarities, in which the cranial and sacral divisions are similar but differ from the thoracolumbar division, the former two divisions have been grouped together as the craniosacral autonomic system in contrast to the thora-

columna. The former is the parasympathetic nervous system, the latter the sympathetic nervous system, according to the common usage of these terms.

The neural structure in the wall of the alimentary canal includes two plexuses, the myenteric and the submucous, which are intimately interconnected and comprise numerous small ganglia. These plexuses, as stated above, have been classified by Langley in a separate division which he called the enteric nervous system. They are ontogenetically, anatomically and physiologically related to the parasympathetic division of the autonomic nervous system, but possess the capacity for independent functional activity in a greater degree than other parts of this system. Their capacity to carry out coördinated reflex activities in the absence of impulses emanating from the central nervous system is well known. The relationships of some of the neurons in the enteric ganglia therefore must differ from those of the neurons in other parts of the autonomic system, e.g., those in the sympathetic trunk ganglia and the autonomic ganglia in the cranial region, which, according to the best available evidence, function only as terminal neurons in visceral efferent chains. It is advantageous because of their anatomical and functional relationships as well as for descriptive purposes to retain the term, enteric nervous system, to designate the plexuses in the wall of the alimentary canal.

Anatomic Structure and Relationships.—Sympathetic Trunks.—Each sympathetic trunk extends from the base of the cranium to the coccyx along the anterolateral aspect of the vertebral column. It is made up of a series of ganglia (vertebral ganglia) connected by longitudinal fibers. Except in the cervical region the ganglia in general are arranged segmentally. They are connected with the spinal nerves through *communicating rami*. The latter include the visceral components of the spinal nerves which are functionally related to the sympathetic system and the sympathetic fibers which join the spinal nerves for distribution to the tissues to be innervated. The spinal nerve components contained in the communicating rami in the main are myelinated and constitute the *white* communicating rami, the sympathetic components, the majority of which either are unmyelinated or but thinly myelinated, constitute the *gray* communicating rami. Visceral components are absent in the cervical, lower three lumbar and first sacral nerves. The communicating rami of these nerves, therefore, include only sympathetic fibers. The visceral nerves through which the internal organs receive their sympathetic innervation arise from the sympathetic trunks. They comprise visceral afferent, preganglionic and sympathetic fibers.

Duncan (1943) has called attention to the erroneous practice of designating the aggregates of sympathetic fibers which join the spinal nerves as rami. Since these fibers join the spinal nerves for their peripheral distribution they constitute roots, according to the common usage of the term. The correctness of this point of view is recognized, but, in view of the almost universal use of the term, gray communicating ramus, the latter will be used in the present volume.

The cervical portion of each sympathetic trunk lies anterior to the transverse processes of the cervical vertebrae and behind the carotid vessels. It includes the superior, middle, intermediate and inferior cervical sympathetic ganglia and contains both myelinated and unmyelinated fibers

The superior cervical, the largest of all sympathetic ganglia, is a somewhat spindle-shaped body located at the base of the skull between the internal carotid artery and the jugular vein and in front of the transverse processes of the second, third and fourth cervical vertebrae. The middle cervical ganglion, which is frequently absent, usually is situated about the level of the body of the sixth cervical vertebra. Not infrequently it occupies a lower position. It commonly lies in front of the inferior thyroid artery, as this artery passes behind the carotid sheath. The intermediate cervical ganglion is relatively small and is located on the medial side of the

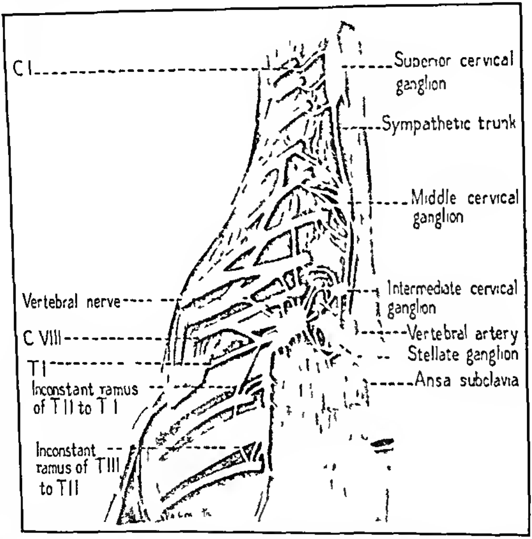

FIG. 4.—Drawing from the cadaver to illustrate the relationships of the cervical and upper thoracic sympathetic trunk ganglia and the inconstant intrathoracic rami of the second thoracic nerve to the first and of the third thoracic nerve to the second

vertebral artery, approximately at the level of the eighth cervical nerve. It is connected with the inferior cervical ganglion by a large ramus which passes behind the vertebral artery and usually by a smaller one which passes in front of this artery. In most cases it is also connected with the inferior cervical ganglion through the ansa subclavia which forms a loop around the subclavian artery (Fig. 4). The inferior cervical ganglion commonly is situated just behind the subclavian artery usually at the point of origin of the vertebral artery. It usually is only imperfectly separated from the first thoracic ganglion, and frequently is fused with the latter

The two when fused constitute the stellate ganglion (Fig. 1), situated anterior to the head of the first rib and behind the pleura.

The *superior cervical* sympathetic ganglion is an elongated body which varies in size within a relatively wide range. It gives rise to gray communicating rami which join the first and second, usually the third and in some instances also the fourth cervical nerves. It also sends gray communicating rami to the hypoglossal nerve, the jugular and nodose ganglia of the vagus, and the petrosal ganglion of the glossopharyngeal nerve. The connections between the superior cervical sympathetic and nodose ganglia, according to Siwe (1931), usually consist of one or two stout rami and several more slender ones. He never observed actual fusion of these two ganglia in man. A peripheral ramus passes behind the carotid sheath to the wall of the pharynx where it joins the ascending pharyngeal plexus. This plexus also receives a few smaller rami from the superior cervical ganglion. Not uncommonly one or two small rami also are supplied to the esophagus. The superior cardiac nerve arises near the lower end of the ganglion and descends behind the large vessels, but usually in front of the superior thyroid artery, and joins the superficial cardiac plexus on the left and the deep cardiac plexus on the right side. It is connected by slender rami with the carotid and external maxillary plexuses and, in some instances, with the sympathetic trunk below the superior cervical ganglion. Rarely it also sends a branch to the recurrent nerve. This branch is joined by a branch from the ansa subclavia. A ramus from the superior cervical ganglion also joins the phrenic nerve. Another joins the common trunk of the superior laryngeal nerve before the latter divides into its internal and external branches. In some instances a ramus which leaves the superior cervical ganglion with the internal carotid nerve also joins the superior laryngeal nerve. The several peripheral rami of the superior cervical ganglion which join the internal carotid artery constitute the internal carotid nerve and give rise to the internal carotid plexus. Other rami join the external carotid artery on which they form a plexus. The plexuses on the carotid arteries represent the major portion of the extension of the sympathetic system into the head.

The *middle cervical* ganglion (Fig. 4), when present, usually is connected by gray rami with the fifth and sixth cervical nerves and sometimes also the fourth and seventh. The middle cardiac nerve arises from this ganglion or, in its absence, from the cervical sympathetic trunk, descends behind the large vessels, either separately or with the other cardiac nerves, and joins the deep cardiac plexus on both sides. Slender rami arising from this ganglion also accompany the inferior thyroid artery to supply the thyroid gland. In the absence of the middle cervical ganglion, the latter also arise directly from the interganglionic cord.

The intermediate cervical ganglion is connected with the brachial plexus by few communicating rami. Frequently a ramus arising from this ganglion joins the sixth cervical nerve and rarely another joins the fifth or the seventh. In instances in which the eighth cervical nerve has a white communicating ramus, some of its preganglionic components probably enter the intermediate cervical ganglion (Kirgis and Kuntz, 1942).

The *inferior cervical* ganglion is connected by gray rami with the seventh and eighth cervical and sometimes also the sixth cervical and first thoracic nerves. In general, the cervical communicating rami lie ventral and

lateral to the vertebral artery, but there exists at least one ramus, the vertebral nerve, which lies dorsal to the vertebral artery (Fig. 4). It connects the ganglion with the sixth or the seventh cervical nerve or both. In the upper part of its course, this nerve sends a few small branches to the plexus on the vertebral artery (Siwe, 1931). The inferior cardiac nerve, arising from the medial side of the ganglion, joins the deep cardiac plexus. Slender rami join the plexuses on the subclavian, internal maxillary and vertebral arteries. Offsets from the plexus on the vertebral artery join the lower cervical nerves not infrequently as high as the fourth. The vertebral rami of the inferior cervical ganglion, therefore, may be regarded as communicating rami. Not infrequently a ramus arising from this ganglion joins the recurrent nerve. In some instances, rami accompany the common carotid artery and, joining the plexus on the internal carotid artery, contribute to the sympathetic innervation of the head. The subclavian plexus, derived mainly from the ansa subclavia, sends rami to the internal mammary artery and the phrenic nerve.

Distal to the nodose ganglion, numerous anastomoses exist between the vagus nerve and the sympathetic trunk but they exhibit no regular arrangement. According to Funaoka (1928), the relationship between the vagus and sympathetic is more intimate on the right side than on the left, particularly in the lower cervical region. He found no anastomoses in this region on the left side in over 50 per cent of the cadavers examined, whereas anastomoses were constantly present on the right side.

In the thorax the sympathetic trunk lies behind the pleura and in front of the necks of the ribs from the first to the tenth. This portion includes ten or eleven ganglia joined together by longitudinal fibers. In most instances the first thoracic ganglion, rarely also the second, is fused with the inferior cervical to form the *stellate* ganglion. Not infrequently other thoracic ganglia are fused so that the number is still further reduced. The thoracic sympathetic ganglia usually are irregularly angular or fusiform but vary greatly both in form and size. In general, they are arranged segmentally.

Each thoracic ganglion is connected with the corresponding spinal nerve by a white and a gray ramus. Sometimes these rami are separate, the white ramus usually leaving the spinal nerve distal to the point at which the gray ramus joins it. Sometimes white and gray rami are intimately fused and constitute a single communicating ramus. Not infrequently the sympathetic ganglion is connected with the spinal nerve by more than two rami. Occasionally one of these ganglia may be connected by communicating rami with more than one spinal nerve. Small ganglia have been observed in some of the gray communicating rami either near their origin from the sympathetic trunk or near the junction with the spinal nerve (Romankevič, 1930, Gruss, 1932, Wrete, 1935). The neurons in these ganglia undoubtedly represent cells which either failed to reach the primordia of the ganglia of the sympathetic trunk during embryological development or became displaced from them.

In a large percentage of cases, an intrathoracic ramus arising from the second thoracic nerve joins the first, usually proximal to the origin of the first intercostal nerve. Not infrequently a gray ramus from the second thoracic sympathetic ganglion joins this ramus. In other cases, a gray ramus joins the second thoracic nerve in proximity to the origin of the

intrathoracic ramus to the first (Fig. 4). The latter ramus receives sympathetic fibers via the gray ramus to the second thoracic nerve, consequently, it constitutes a pathway through which sympathetic fibers which leave the sympathetic trunk below the first thoracic ganglion enter the brachial plexus (Kuntz, 1927). In a somewhat smaller percentage of cases, a ramus arising from the third thoracic nerve just distal to its communicating rami joins the second thoracic nerve in proximity to the origin of the ramus of the latter nerve which joins the first thoracic (Kirgis and Kuntz, 1942). This ramus was demonstrated bilaterally in 15 and unilaterally in 18 of 41 cadavers examined. It includes unmyelinated fibers undoubtedly of sympathetic origin which enter it via the gray communicating ramus of the third thoracic nerve. In some instances such fibers could be traced from this ramus directly into the ramus of the second thoracic nerve which joins the first. These rami consequently constitute a pathway through which sympathetic fibers arising in the third thoracic segment or lower may reach the brachial plexus without traversing the upper thoracic sympathetic trunk ganglia (Fig. 4).

Peripheral rami arising from the upper five thoracic ganglia supply the upper part of the aorta. The second, third and fourth thoracic ganglia also send rami into the cardiac and posterior pulmonary plexuses. The *splanchnic* nerves consist mainly of visceral afferent and preganglionic visceral efferent fibers which join the sympathetic trunk *via* the white rami and merely traverse it on their way to more peripheral ganglia incorporated in the prevertebral plexuses or located in proximity to the viscera. The *greater splanchnic* nerve is formed by the union of several rami arising from the sympathetic trunk between the fifth and ninth or tenth thoracic ganglia (Fig. 5). In some instances a ganglion is present in the course of this nerve (Streckfuss, 1931). Descending in the posterior mediastinum it pierces the diaphragm and joins the celiac ganglion. A slight enlargement, the splanchnic ganglion, occurs on this nerve opposite the eleventh or twelfth thoracic vertebra. Rami arising both from this ganglion and the nerve join the esophagus and the descending aorta. The *lesser splanchnic* nerve is formed by the union of several rami arising usually from the ninth and tenth thoracic ganglia. It pierces the diaphragm in proximity to the greater splanchnic nerve and, entering the celiac plexus terminates in the aorticorenal ganglion. The *lowest splanchnic* nerve (sometimes absent) arises from the last thoracic ganglion or the lesser splanchnic nerve, pierces the diaphragm and terminates in the renal plexus.

Passing from the thorax into the abdomen, the sympathetic trunk usually lies between the lateral and medial crura of the diaphragm (Labbock, 1932). At this level it is a very slender cord. In the lumbar region it lies upon the bodies of the vertebrae, anterior to the lumbar vessels and medial to the origin of the psoas major muscle. The right and left trunks are interconnected in this region by numerous slender rami (Fig. 6) and rarely are symmetrical. Not infrequently one or both trunks are separated into two or more strands for varying distances. Perlow and Vehe (1935) observed such separation in 9 of 48 lumbar trunks. In such cases ganglia may be associated with all the strands. The lumbar portion of each trunk usually includes four ganglia but the number varies from two to eight (Romankevič, 1930). Occasionally the lumbar ganglia are fused to such an extent that it becomes impossible to recognize individual ganglia. The

first and second lumbar spinal nerves and occasionally the third send white communicating rami into this portion of the sympathetic trunk. It also contains myelinated fibers which enter the trunk through the white communicating rami of the lower thoracic nerves and extend downward. Gray communicating rami arising from the lumbar portion of the sympathetic

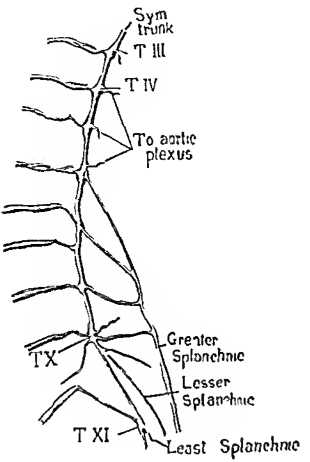

FIG 5

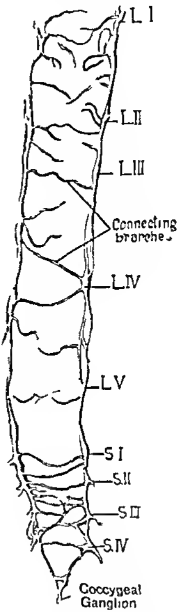

FIG 6

FIG 5.—Thoracic sympathetic trunk, communicating rami, rami to aortic plexus, and splanchnic nerves.

FIG 6.—Lumbar and sacral sympathetic trunks. (Drawn from photographs of dissections of human cadavers by permission of Dr J D Humber.)

trunk join all the lumbar nerves. These rami also are extremely variable. One ramus may bifurcate and join two adjacent spinal nerves, or several gray rami (two to five) may join a single spinal nerve. In 65 per cent of the cases examined by Romankevič, ganglia were present in the communicating rami. Peripheral rami from this portion of the sympathetic trunk also join the aortic plexus.

Continuing into the pelvis the sympathetic trunk lies on the pelvic surface of the sacrum medial to the anterior sacral foramina (Fig 6) The right and left trunks are connected with each other by frequent connecting rami Tending toward the median plane, both trunks usually terminate in the ganglion impar, or coccygeal ganglion, on the surface of the coccyx This portion of the sympathetic trunk usually includes four ganglia, but the number may vary from two to six (Lablock 1937) The ganglia are small and gradually diminish in size from above downward The sacral portions of the sympathetic trunks are not strictly symmetrical and in some instances a secondary trunk, with several small ganglia extending from the first sacral segment to the third may be demonstrated on one or both sides (Lablock 1938) Like the cervical and lower lumbar portions of the sympathetic trunk this portion receives no white communicating rami The third and fourth sacral nerves and occasionally the second or fifth (Sheehan, 1941) include visceral components which enter the pelvic plexus via the visceral rami of these nerves without passing through the sympathetic trunk Gray rami arising from the pelvic portion of the sympathetic trunk join both the sacral and coccygeal nerves Visceral rami of small size also join the pelvic plexus A few small parietal rami from both sides form a plexiform network over the pelvic surface of the sacrum

Prevertebral Plexuses —The prevertebral autonomic plexuses are situated in the thorax, abdomen and pelvis Four of these, the *cardiac, celiac, hypogastric* and *pelvic* plexuses may be regarded as the great prevertebral plexuses to each of which smaller plexuses are subsidiary

The Thoracic Plexuses —The Cardiac Plexus is situated at the base of the heart and consists of a superficial and a deep part It is connected with the sympathetic trunks through the superior, middle and inferior cervical and a variable number of thoracic cardiac nerves, and receives branches of both vagi The structure and peripheral distribution of this plexus will be described in Chapter VII

The Pulmonary Plexuses are continuous with the cardiac plexus, but not subsidiary to it They are intimately related to the vagus nerves, through which they *receive preganglionic fibers* They will be described in detail in Chapter IX

Mediastinal Ganglia —In addition to the ganglia incorporated in the cardiac and pulmonary plexuses, minute aggregates of ganglion cells occur scattered in the mediastinum In some instances, one or more larger aggregates of ganglion cells are present In three cadavers, Teitelbaum and Uhlenhuth (1932) described a ganglion of considerable size, which they called the mediastinal ganglion, located in the posterior mediastinum, ventral to the descending aorta and just below the level of the root of the left lung It is connected with both vagi and sends branches to the trachea, bronchi and esophagus Ganglion cells in the mediastinum which are not incorporated in the cardiac and pulmonary plexuses probably should be regarded as sympathetic

The Abdominal and Pelvic Plexuses —The celiac, hypogastric and pelvic plexuses are closely associated with the abdominal aorta and the hypogastric arteries The subsidiary plexuses extend out on the branches of these arteries and in the main are named after them They are made up largely of the fibers arising from their intrinsic ganglia and peripheral

rami from the lower thoracic, lumbar and upper sacral portions of the sympathetic trunks. Branches of the right vagus nerve also contribute to the celiac plexus and the visceral rami of the third and fourth sacral nerves join the pelvic plexus without traversing the sympathetic trunk. The hypogastric plexus is continuous with the celiac plexus superiorly and with the pelvic plexus inferiorly. Nerves are distributed through these plexuses to the viscera and vessels of the abdominal and pelvic cavities.

On the basis of a comparative study of the prevertebral plexuses in man and other primates, Hartmann-Weinberg (1926) pointed out that the series of plexuses along the abdominal aorta, although they exhibit a relatively wide range of variation, fundamentally consist of two paired chains: a central and a lateral pair. Each chain is made up of a metameric series of ganglia connected with one another by interganglionic rami. The several chains are connected with one another and with the sympathetic trunks in a more or less regular manner. They also receive branches of the right vagus and give rise to branches which supply the abdominal and pelvic viscera. The visceral rami of each chain have a more or less definite distribution. Those arising from the central chain supply the liver, pancreas, spleen and digestive tube from the abdominal portion of the esophagus to the upper part of the rectum. The lateral chain gives rise to rami which supply the adrenals and the urogenital system. Some of these rami also supply fibers to the large intestine. The aorta and the paired arteries arising from it which extend into the body wall receive their nerve supply directly from the sympathetic trunks.

The Celiac (Solar) Plexus is the most extensive of the prevertebral plexuses. It is closely associated with the aorta and surrounds the celiac artery. It comprises a dense meshwork of fiber bundles, two large aggregates of ganglion cells, the celiac ganglia, and a number of smaller ganglia. The right and left celiac ganglia lie on the right and left crura of the diaphragm, respectively. They receive the greater splanchnic nerves and constitute the chief ganglionic centers of the celiac plexus. The lesser splanchnic nerves enter the aortico-renal ganglia which may be regarded as partially detached portions of the celiac ganglia at their inferior poles.

The celiac plexus (Fig. 7) invests the celiac artery throughout its entire length and is continuous with the subsidiary plexuses along its branches. The latter include the *left gastric* plexus, from which rami extend to the esophagus and stomach, the *hepatic plexus*, from which rami extend to the liver and gall bladder, stomach, duodenum and pancreas and the *splenic plexus*, from which rami extend to the spleen, the pancreas and the stomach.

Nerves arising from the celiac ganglia and plexus form subordinate plexuses on the aorta and its branches. The *phrenic* plexus accompanies the inferior phrenic artery. It supplies the diaphragm and gives off rami to the adrenal plexus. On the left side it also supplies rami to the esophagus, on the right, to the inferior vena cava. The *adrenal* plexus accompanies the adrenal artery and sends rami into the substance of the adrenal gland. The *renal* plexus extends lateralward along the renal artery to the hilum of the kidney. It is connected with the adrenal plexus and also receives the lowest splanchnic nerve. The *pancreatic plexus* is closely associated with the head and body of the pancreas. In part it is derived directly from the celiac plexus. It also is connected with the superior mesenteric, aortic, hepatic and duodenal plexuses. The *duodenal plexus* is a delicate

meshwork of fibers without macroscopic ganglia located in the retroperitoneal tissue behind the pancreas It is derived mainly from the pancreatic and superior mesenteric plexuses (Kiss and Ballon 1929) The *superior mesenteric* plexus accompanies the superior mesenteric artery and forms subordinate plexuses on its branches, through which fibers are supplied

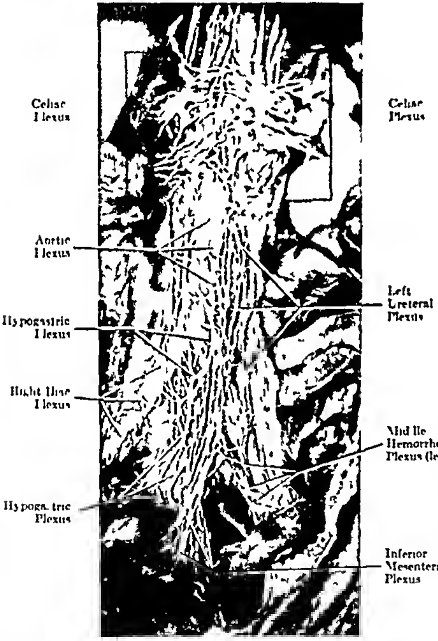

FIG 7 —Photograph of human dissection (By permission of Dr J D Humber)

to the small intestine cecum, vermiform appendix and ascending and transverse portions of the colon This plexus includes the superior mesenteric ganglion and is continuous inferiorly with the aortic plexus The *aortic* plexus invests the abdominal aorta It may be regarded as a continuation of the celiac plexus downward but it also receives rami from the lumbar sympathetic trunk and is connected with the hypogastric plexus

by the hypogastric nerves It contributes rami to the adrenal and renal plexuses and gives rise to the spermatic (or ovarian) and the inferior mesenteric plexuses The *spermatic* plexus also receives rami from the renal plexus and extends along the spermatic artery into the spermatic cord and testis The *ovarian* plexus accompanies the ovarian artery into the pelvis It supplies rami to the ovary and uterine tube and through its communication with the uterine plexus, to the uterus The *inferior mesenteric* plexus invests the inferior mesenteric artery and is continuous with the subordinate plexuses on its branches the colic sigmoid and superior hemorrhoidal plexuses through which rami are supplied to the descending colon and the upper part of the rectum (Fig 7)

The Hypogastric Plexus connects the celiac and pelvic plexuses As the hypogastric nerves descend into the pelvis they break up into numerous bundles which form a plexiform meshwork along the front and back of the bifurcation of the aorta and the region of the common iliac arteries and over the promontory of the sacrum This meshwork constitutes the hypogastric plexus (Fig 7)

The Pelvic Plexuses are located along either side of the rectum They receive the visceral rami of the sacral nerves which convey preganglionic fibers in addition to rami from the upper sacral portions of the sympathetic trunks Each pelvic plexus is continuous with its subordinate plexuses accompanying the hypogastric artery and its branches the hemorrhoidal vesical, prostatic or uterine and vaginal plexuses, through which fibers are supplied to the pelvic viscera

The Enteric Plexuses extend throughout the length of the alimentary tract from the upper level of the esophagus to the anal canal They comprise the myenteric plexus situated between the longitudinal and circular muscles, and the submucous plexus in the submucosa These plexuses are intimately connected with each other through numerous connecting rami Postganglionic fibers derived from the prevertebral plexuses traverse the enteric ganglia and contribute to the plexuses The preganglionic fibers to the enteric ganglia are components of the vagus and sacral nerves The enteric plexuses will be described in detail in Chapter X

Cephalic Sympathetic Plexuses—The cephalic sympathetic plexuses may be regarded as an extension of the sympathetic trunk into the cephalic region Rami arising from the superior cervical sympathetic ganglion extend along the internal and external carotid arteries respectively as the internal and external carotid nerves The internal carotid rami become applied to the internal carotid artery as it enters the carotid canal in the temporal bone As they continue cephalad they become separated into lateral and medial divisions The lateral division gives rise to the *internal carotid* plexus which invests the internal carotid artery The medial division gives rise to the *cavernous* plexus associated with the cavernous sinus The external carotid rami form the plexus on the external carotid artery (Fig 8)

The Internal Carotid Plexus sends communicating branches to the abducens nerve and the semilunar ganglion It also gives rise to the deep petrosal and caroticotympanic nerves The deep petrosal nerve joins the greater superficial petrosal to form the nerve of the pterygoid canal which terminates in the sphenopalatine ganglion The caroticotympanic nerves join the tympanic plexus

The Cavernous Plexus sends communicating branches to the oculomoto trochlear and ophthalmic nerves and the ciliary ganglion It also supplies fibers to the hypophysis

The Tympanic Plexus is formed mainly by the caroticotympanic nerve and a tympanic ramus arising from the petrosal ganglion It is situated on the medial wall of the middle ear and supplies fibers to the mucous membrane of the tympanum, mastoid cells and auditory tube A slender ramus made up mainly of fibers which enter this plexus through the tympanic ramus from the petrosal ganglion unites with a ramus from the genicula

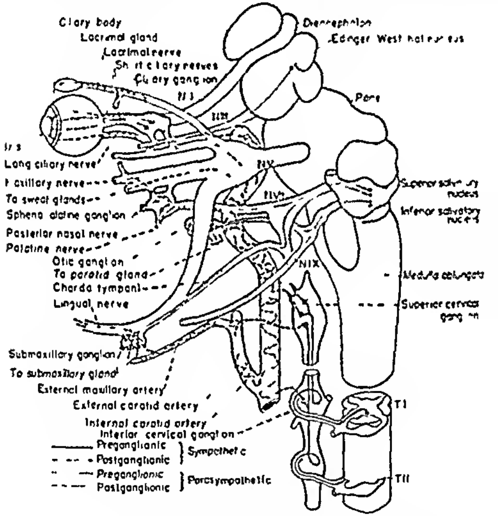

FIG 8 — Diagrammatic illustration of the relationships of the sympathetic and parasympathetic nerves in the cephalic region

ganglion of the nervus intermedius to give rise to the lesser superficial petrosal nerve which passes through the temporal bone and joins the otic ganglion

The External Carotid Plexus is made up of the external carotid rami from the superior cervical sympathetic ganglion It accompanies the external carotid artery and gives rise to subordinate plexuses on the branches of this artery It also supplies rami to the glomus caroticum The subordinate plexuses on the middle meningeal and external maxillary arteries supply rami to the otic and submaxillary ganglia respectively

The Common Carotid Plexus — The plexus on the common carotid artery is continuous superiorly with the internal and external carotid plexuses It includes fibers arising in the inferior and middle cervical sympathetic ganglia and afferent components of the upper thoracic spinal nerves Many of the latter extend cephalad and become associated with the cephalic sympathetic nerves (Kuntz, 1934)

Cephalic Autonomic Ganglia —The major cephalic autonomic ganglia are situated in relation to the oculomotor nerve and the several divisions of the trigeminal nerve, but are related functionally to the nerves through which they receive preganglionic fibers (Fig 8)

The Ciliary Ganglion is a small reddish ganglion located in the posterior portion of the orbit, between the lateral rectus muscle and the optic nerve, and in proximity to the ophthalmic artery It is connected with the inferior division of the oculomotor nerve by a short *motor* root through which it receives preganglionic fibers and with the nasociliary branch of the ophthalmic nerve by a long *sensory* root It also receives a slender ramus the *sympathetic* root derived from the cavernous plexus This ramus may join the ciliary ganglion as an independent root or it may be incorporated in the long root from the nasociliary nerve Twelve to fifteen slender rami the *short ciliary* nerves arise from the ciliary ganglion and passing forward above and below the optic nerve convey fibers to the eye its extrinsic muscles and the blood vessels

Like the other major cephalic autonomic ganglia, the ciliary ganglion is essentially parasympathetic Among the early investigators Arnold (1831) and Rauber (1872) classified it as autonomic Reichert (1875) described bipolar neurons in it, and Schwalbe (1879) and van Gehuchten (1893) regarded it as sensory Krause (1882) Burkheimer (1879), Fritz (1899) and Marina (1901) regarded it as made up in part of sensory and in part of motor neurons Michel (1894) Retzius (1894), Marinesco Parhon and Goldstein (1908) Sala (1910) Muller and Dahl (1910) and Carpenter (1911) observed only multipolar neurons in this ganglion and regarded it as purely autonomic (parasympathetic) Pines (1927) described ganglion cells of eight morphological types in the ciliary ganglion in man, including some bipolar and some unipolar neurons Pines and Friedman (1929) described ganglion cells of essentially the same morphological types in the ciliary ganglion in the monkey and certain other mammals but in varying proportions The multipolar ganglion cells were predominant in all their preparations

In an intensive study of the ciliary ganglion of the cat, Christensen (1932) recognized ganglion cells of most of the morphological types described by Pines and Friedman but none which could be regarded either as bipolar or unipolar He observed some with only two and some with only one large process but all of these showed additional very small cytoplasmic processes

The Sphenopalatine Ganglion is a small reddish ganglion located in the sphenopalatine fossa, close to the sphenopalatine foramen and at the peripheral end of the nerve of the pterygoid canal, through which it receives both preganglionic (motor root) and sympathetic (sympathetic root) fibers The preganglionic fibers are components of the facial nerve and are conveyed to the nerve of the pterygoid canal via the greater superficial petrosal nerve The sympathetic fibers are derived from the plexus

in the internal carotid artery and join the nerve of the pterygoid canal through the deep petrosal nerve. Branches of the maxillary nerve join the sphenopalatine ganglion and constitute its sensory roots.

On the basis of clinical observations, Sluder (1920) suggested the possibility that the sphenopalatine ganglion may include some ganglion cells which are afferent in function. Dehe (1927) advanced the opinion that this ganglion is not purely autonomic but in part of vagus origin. He also maintained that the nerve of the pterygoid canal includes fibers of vagus origin. Recent anatomical studies do not support the opinion that the sphenopalatine ganglion includes afferent ganglion cells. The assumption that the nerve of the pterygoid canal includes fibers of vagus origin is supported both by clinical (Ivy, 1932) and anatomical (Kuntz, 1934) data indicating the existence of vagus fibers in the cephalic sympathetic nerves.

Peripheral rami arising from the sphenopalatine ganglion are distributed as follows. A *pharyngeal* ramus, passing backward through the pharyngeal canal, supplies the mucous membrane of the roof of the pharynx. Three palatine nerves reach the palate through the palatine canals. The *anterior* or *great palatine* nerve gives rise to anterior filaments which reach the incisor teeth and communicate with branches of the nasopalatine nerve. In the palatine canal it gives rise to a small ramus, the *posterior inferior lateral nasal* nerve, which supplies the mucous membrane of the inferior concha. The *middle* or *external palatine* and *posterior* or *small palatine* nerves supply the mucous membrane of the soft palate, uvula and palatine tonsil. A small ramus, the *posterior superior lateral nasal* nerve, supplies the mucous membrane of the middle and superior conchae. The *nasopalatine* nerve supplies the mucous membrane of the hard palate and the roof and septum of the nose. One or more *orbital* rami also pass upward from the sphenopalatine ganglion to the periosteum of the orbit. Some fibers of these rami also join terminal branches of the ophthalmic nerve (Vogel, 1930).

The Otic Ganglion is a small ganglion located medial to the mandibular nerve just below the foramen ovale and at the posterior border of the pterygoid muscle. Its preganglionic (motor root) fibers are components of the glossopharyngeal nerve and are conveyed to the ganglion via the lesser superficial petrosal nerve which also constitutes its sensory root. Reichert and Poth (1933) advanced certain data which seem to indicate that some preganglionic components of the facial nerve also enter the otic ganglion in man.

Its sympathetic root is derived from the plexus on the middle meningeal artery. Communicating rami arising from the otic ganglion join the nerve of the pterygoid canal, the auriculotemporal nerve and the chorda tympani. It also sends peripheral rami to the tensor tympani and tensor veli palatini muscles.

The Submaxillary Ganglion is a small reddish ganglion located between the lingual nerve and the duct of the submaxillary gland. Its preganglionic (motor root) fibers are components of the facial nerve which join the lingual nerve via the chorda tympani. According to Reichert and Poth some preganglionic components of the glossopharyngeal nerve also enter the submaxillary ganglion in man.

Its sensory root, made up mainly of components of the nervus inter-

medius joins the ganglion as a slender ramus of the lingual nerve. Its sympathetic root is derived from the plexus on the external maxillary artery. Peripheral rami arising from the submaxillary ganglion supply the submaxillary gland and its duct. Other peripheral fibers join the lingual nerve and are conveyed to the sublingual gland.

The Lingual Ganglia comprise numerous small aggregates of autonomic ganglion cells located between the intrinsic muscles in the posterior portion of the tongue. They lie mainly within the range of distribution of the glossopharyngeal nerve, through which they probably receive *preganglionic fibers*.

The Ganglion Terminale is made up in part of autonomic ganglion cells (Brookover, 1914, 1917, Larsell, 1918). The sources of the preganglionic fibers related to these cells have not been clearly delimited but the fibers undoubtedly emerge from the forebrain as efferent components of the nervus terminalis. The peripheral branches of this nerve are distributed mainly to the anterior cerebral artery and its branches and the mucous membrane of the nasal septum, including the vomeronasal organ.

Other Ganglia. — An accessory sympathetic ganglion located in relation to the internal carotid artery and in the course of the internal carotid nerve has been described in man by Chorobski and Penfield (1932). A ganglion located in the corresponding position and in the course of the internal carotid nerve also has been observed in the cat. This ganglion probably comprises nerve cells which have been displaced from the primordium of the superior cervical sympathetic ganglion. Gellert (1931) described several small ganglia in the portion of the internal carotid plexus which passes through the cavernous sinus. The fibers arising in these ganglia, with other fibers of the internal carotid plexus, enter the ophthalmic nerve.

Chorobski and Penfield also described an aggregate of ganglion cells located at the junction of the greater superficial petrosal nerve with the internal carotid nerve in man. They reported experimental data in support of the assumption that preganglionic components of the greater superficial petrosal nerve effect synaptic connections with these cells, consequently, they represent a parasympathetic ganglion. Their experimental findings support the assumption that scattered ganglion cells, some of which are incorporated in sympathetic and others in parasympathetic efferent conduction pathways, occur along the internal carotid and cerebral arteries.

An aggregate of ganglion cells located on the surface of the pineal body and just beneath the chorioid plexus in a full term human fetus was described by Marburg (1909). Pastori (1929) also described a small autonomic ganglion located at the tip of the pineal body. According to her account, this ganglion comprises approximately 30 ganglion cells and is connected by nerve fibers with the pineal body and the cerebral blood vessels. Levin (1938) described a complex of ganglion cells and nerve fibers within the pineal body in monkeys of several different species. This structure, which comprises approximately 2000 ganglion cells, is connected with the posterior and habenular commissures and the tela chorioidea. This obviously is not the nervous complex described by Pastori. Its connections with the tela chorioidea suggest autonomic relationships but in view of its intramedullary connections, it cannot be regarded as wholly autonomic.

Other Ganglia Associated with the Cranial Autonomic Nerves.—The geniculate ganglion of the nervus intermedius, the petrosal ganglion of the glossopharyngeal and the jugular and nodose ganglia of the vagus nerve are intimately associated with the cranial autonomic nerves and have been regarded by some as in part autonomic.

The *geniculate* ganglion is situated in the facial canal at the genu of the facial nerve. From it arise three slender rami. (1) The greater superficial petrosal nerve contains chiefly preganglionic fibers to the sphenopalatine ganglion and sensory fibers which traverse this ganglion to be distributed through the middle and posterior palatine nerves to the mucous membrane of the soft palate. (2) The geniculotympanic nerve enters the tympanic plexus and, continuing through the latter, joins the small superficial petrosal nerve. (3) The external superficial petrosal nerve is an inconstant ramus which joins the sympathetic plexus on the middle meningeal artery. The *petrosal* ganglion is situated in the lower part of the jugular foramen. It receives a ramus from the superior cervical sympathetic ganglion and gives off a ramus which passes into the tympanic plexus and emerges as the small superficial petrosal nerve. The *jugular* and *nodose* ganglia of the vagus are intimately associated with the superior cervical sympathetic ganglion. Their connections with the latter ganglion are described above.

All of these ganglia are traversed by preganglionic fibers and include afferent neurones which are functionally related to the autonomic nerves. Certain histological findings have been interpreted as supporting the assumption that they include autonomic ganglion cells. Synaptic connections within the ganglia, however, have not been demonstrated. In view of all the data available, these ganglia, like the other cerebrospinal ganglia, must be regarded as comprising only sensory ganglion cells.

Components and Structure of the Sympathetic Trunks.—Each sympathetic trunk comprises of a series of ganglia, the vertebral ganglia, and the connecting internodal rami. The latter consist primarily of visceral afferent and preganglionic visceral efferent fibers which enter the sympathetic trunk through the white communicating rami. The preganglionic neurons are located in the intermediolateral cell column and adjacent parts of the gray matter throughout the thoracic and upper lumbar regions of the spinal cord. Their axons enter the sympathetic trunk via the white communicating rami and either terminate in one of its ganglia in synaptic relationship to sympathetic ganglion cells or traverse the trunk for a shorter or longer distance and continue peripheralward in one of its branches to terminate in a sympathetic ganglion lying nearer a visceral organ. The visceral afferent neurons which send fibers into the sympathetic trunk are components of the posterior nerve roots. These fibers enter the sympathetic trunk via the white rami and traverse it without making synaptic connections with sympathetic neurons. Throughout the greater part of the sympathetic trunk the internodal rami also contain some fibers which arise from sympathetic ganglion cells and run longitudinally for a shorter or longer distance before entering the nerves through which they are conveyed to their peripheral destination. Every gray communicating ramus probably receives fibers from one or two ganglia above and below as well as from the ganglion in the segment of the sympathetic trunk from which it arises (Takagi, 1929).

The preganglionic and visceral afferent fibers which make up the cervical

internodal rami enter the sympathetic trunk via the white communicating rami of the upper five or six thoracic nerves. According to various investigators, including Ranson and Billingsley (1918), Bluer (1930) and Cleveland (1932), the upper portion of the cervical sympathetic trunk contains no afferent fibers, consequently, the upper internodal ramus consists almost exclusively of preganglionic fibers which terminate in the superior cervical sympathetic ganglion. In sections of the sympathetic trunk taken just below the superior cervical ganglion, fascicles of unmyelinated fibers not infrequently are observed at the periphery of the internodal ramus. These fibers do not degenerate following section of the trunk in the lower cervical levels, they obviously are postganglionic fibers which arise in the superior cervical ganglion and extend in the internodal ramus for a short distance before entering a peripheral ramus of distribution. The possibility that some of these fibers may be the axons of commissural neurons is not precluded but evidence that commissural neurons occur in the sympathetic trunk is wanting. Exclusive of such inconstant peripheral fascicles of postganglionic fibers nearly all the fibers in this portion of the sympathetic trunk are myelinated. They are of relatively small caliber and closely aggregated. In the cat, the majority of these fibers according to measurements carried out by Ranson and Billingsley (1918), vary from 1.5 to 3.5 microns in diameter. They found relatively few fibers with a diameter greater than 4.5 microns and occasional ones with a diameter of 6.5 or 7 microns. All these fibers undergo degeneration toward the superior cervical ganglion following section of the sympathetic trunk at any level in the neck.

After section of the communicating rami of the first and second thoracic nerves and the sympathetic trunk below the stellate ganglion Langley (1896, 1900) found no intact myelinated fibers in the cervical sympathetic trunk. He therefore, concluded that no myelinated fibers run from one of the cervical sympathetic ganglia to another or enter the sympathetic trunk through cervical communicating rami. Ranson and Billingsley (1918) concurred in this conclusion. Preganglionic fibers probably do not pass through the superior cervical ganglion into the nerves arising from it except to reach the sympathetic ganglion on the internal carotid artery and such scattered sympathetic ganglion cells as may occur along the internal carotid and cerebral arteries.

Below the middle cervical ganglion or the origin of the middle cardiac nerve, the cervical sympathetic trunk contains both preganglionic and visceral afferent fibers. The majority of the latter are conveyed to their peripheral destination through the middle and inferior cardiac nerves and rami arising from the ansa subclavia to be distributed to the heart and lungs.

Throughout the thoracic and lumbar regions, the sympathetic trunk contains both preganglionic and visceral afferent fibers. These fibers, most of which are myelinated, are arranged in a compact bundle, usually oval in cross-section. Unmyelinated fibers occur only in small numbers above the fourth thoracic ganglion. Below this level they are more abundant and are arranged in a crescent-shaped fascicle at the periphery of the larger oval fascicle of myelinated fibers. The crescent-shaped fascicle is made up of fibers which arise in the ganglia of the sympathetic trunk

and run longitudinally for a shorter or longer distance before entering a ramus of distribution (Ranson and Billingsley, 1918).

Above the sixth thoracic ganglion, most of the fibers in the sympathetic trunk are ascending preganglionic fibers which terminate in the upper thoracic and cervical ganglia. The lowest source of preganglionic fibers to the superior cervical ganglion is the seventh thoracic nerve. Fibers which enter the sympathetic trunk through white rami as low as that of the ninth thoracic nerve are known to reach the inferior cervical ganglion. From the sixth thoracic ganglion to the ninth the sympathetic trunk contains both ascending and descending preganglionic fibers. Below the tenth thoracic ganglion it contains chiefly descending preganglionic fibers from the lower thoracic and lumbar nerves to the more caudal ganglia of the trunk and the splanchnic nerves. The highest source of preganglionic fibers which enter the splanchnic nerves is the fifth, possibly the fourth, thoracic nerve. Fibers which enter the sympathetic trunk through a given white ramus may be distributed to from five to ten successive ganglia, although any one preganglionic fiber probably does not give off branches to so large a number of ganglia. These statements regarding the distribution of preganglionic fibers are based on Langley's (1892, 1900, 1903) findings in the cat, which in general corroborate and extend Gaskell's (1886) earlier findings in the dog. Müller (1909) has shown that the sympathetic trunk in man exhibits a similar distribution of preganglionic fibers.

Ranson and Billingsley (1918) presented evidence which indicates that the visceral afferent components of the sympathetic trunk are chiefly myelinated fibers of large and medium sizes, but that small myelinated and unmyelinated visceral afferent fibers also occur. The latter are not easily distinguished from the preganglionic fibers. Large and medium-sized myelinated fibers are present in varying numbers in different parts of the thoracic sympathetic trunk. They are relatively few above the sixth thoracic ganglion, and gradually increase in number below this level until the roots of the greater splanchnic nerve are reached, through which a large proportion of these fibers is conveyed to the viscera. Afferent components of the splanchnic nerves enter the spinal cord via the white communicating rami of all the spinal nerves from the third thoracic to the first lumbar inclusive (Bain, Irving and McSwiney, 1935). Large and medium-sized myelinated fibers are present in relatively small numbers in the sympathetic trunk below the roots of the splanchnic nerves. Some of these fibers continue downward into the sacral region.

The unmyelinated fibers which enter the sympathetic trunk through white rami, according to Ranson and Billingsley, have a distribution similar to that of the myelinated ones which they regarded as sensory, and are arranged in bundles between the myelinated fibers in the oval fascicle. They occur only in small numbers in the upper thoracic segments, but are present in greater abundance in those segments of the sympathetic trunk in which the large and medium-sized myelinated fibers are more numerous. The possibility that some of the unmyelinated fibers are preganglionic axons which have lost their myelin sheaths is not precluded by the data here presented, but Ranson and Billingsley (1918) have demonstrated, by degeneration experiments, that they are fibers which take origin from cells in the spinal ganglia.

In the sacral region, the sympathetic trunk contains both myelinated and unmyelinated fibers. A crescent-shaped fascicle like the one described in the thoracic region does not occur here but the unmyelinated fibers run in bundles among the myelinated ones. Most of them are descending components of the lower thoracic and upper lumbar nerves (Johnson, 1921). They include both preganglionic and visceral afferent fibers. According to Johnson, large myelinated fibers also enter the sacral sympathetic trunk through the gray rami of the lower lumbar and sacral nerves. He demonstrated by degeneration experiments that these are dorsal root fibers and therefore afferent in character. The possibility that dorsal root fibers may enter the sympathetic trunk through gray rami was pointed out by Langley (1896) but he did not anticipate that they do so in such large numbers as is indicated by Johnson's observations.

The results of an experimental anatomical study reported by Kuntz and Farnsworth (1928, 1931) support the assumption that the gray communicating rami joining the brachial and lumbosacral plexuses include myelinated fibers of relatively large, medium and small sizes, in addition to the unmyelinated ones. The myelinated fibers of large and medium sizes undergo degeneration following section of both roots of the thoracic and upper lumbar nerves distal to the spinal ganglia or section of the white communicating rami and the sympathetic trunk proximal to the ganglia from which the gray rami in question arise. Since no efferent fibers are known to pass through the sympathetic trunk into the gray communicating rami, the fibers in the gray rami which undergo degeneration following the sections indicated above must be regarded as components of the dorsal roots of the thoracic and upper lumbar nerves which traverse the sympathetic trunk and gray communicating rami to join the somatic rami of the spinal nerves for peripheral distribution. The afferent fibers which enter the brachial and lumbosacral plexuses respectively, through the sympathetic trunk and gray rami probably arise in the spinal ganglia connected with the segments of the spinal cord from which the corresponding preganglionic efferent fibers emerge.

In an experimental study of the distribution of fibers of spinal origin in the sympathetic trunks by means of the degeneration method, Matsui (1925) observed, following section of the roots of one or more thoracic nerves in the dog, that in some instances a small number of fibers also underwent degeneration in the sympathetic trunk on the unoperated side. He concluded that preganglionic fibers which enter the sympathetic trunk on one side, in some instances, cross over in small numbers and enter the sympathetic trunk on the opposite side. The paths through which such fibers reach the opposite sympathetic trunk were not determined but they probably traverse the rami which connect the sympathetic trunks.

Ratio of Preganglionic to Ganglionic Neurons.—Quantitative studies of various autonomic ganglia and the preganglionic fibers which enter them indicate that the neurons in the ganglia outnumber the preganglionic fibers. A single preganglionic axon, consequently, must effect synaptic connections with more than one autonomic ganglion cell. Extensive data bearing on the ratio of preganglionic fibers to autonomic ganglion cells are not available, but isolated studies bearing on this ratio have been reported. On the basis of carefully executed actual counts of the ganglion cells in the superior cervical sympathetic ganglion and the myelinated nerve fibers in

sections of the sympathetic trunk taken between the superior and middle cervical ganglia in the cat, Billingsley and Ranson (1918) concluded that the ratio of preganglionic fibers to ganglion cells, in this instance, is approximately 1 to 32. In the light of more recent studies, it seems highly probable that the fibers counted by these investigators did not include all the preganglionic fibers present in the cervical segments of the sympathetic trunk. Foley and Du Bois (1940) have pointed out on the basis of studies carried out on material prepared by a modification of the pyridine silver technic and osmic acid preparations that in some cats 5 to 60 per cent of the preganglionic fibers in the cervical portion of the sympathetic trunk may be unmyelinated. Certain data reported by Kiss and Zador (1941) indicate that in the cat some postganglionic fibers also are thinly myelinated. In a study carried out by Wolf (1941) the ratio of the preganglionic fibers in the cervical sympathetic trunk to the ganglion cells in the superior cervical sympathetic ganglion in the cat was found to be 1 to 11 in one animal and 1 to 17 in another. In the same study the ratio of the preganglionic fibers which enter the ciliary ganglion to the ganglion cells in that ganglion was found to be approximately 1 to 2.

The ratio determined on the basis of actual counts of the ganglion cells and the preganglionic fibers which enter a ganglion is not necessarily an accurate indication of the average number of ganglion cells with which a single preganglionic fiber effects synaptic contacts, since the result may be vitiated by other factors. Intraganglionic commissural neurons are not precluded, although strong evidence has been advanced against the occurrence of either inter- or intraganglionic commissural neurons in the sympathetic trunk. Lawrentjew (1924) described fiber terminations in the form of pericellular apparatuses on neurons in the superior cervical ganglion in the cat which remained intact eight to thirty days after isolation of the ganglion by section of all its rami including the upper internodal ramus of the sympathetic trunk. He interpreted these structures as the terminations of collaterals arising from the axons of neurons within the superior cervical ganglion. He also observed pericellular apparatuses in preparations of the superior mesenteric ganglion nine to fifteen days after section of all its afferent connections. Pines (1927) also described the terminations of collaterals arising near the base of the axon of one neuron on the cell body of an adjacent one in the ciliary ganglion in man. In view of all the evidence to the contrary these findings cannot be accepted without further confirmation. If the intraganglionic connections described by Lawrentjew and Pines actually exist, it is unnecessary to assume that preganglionic fibers make direct synaptic connections with all the autonomic ganglion cells. On the other hand, it is not unreasonable to assume that a single preganglionic fiber may make direct synaptic connections with several or many autonomic ganglion cells.

CHAPTER II

AUTONOMIC GANGLION CELLS AND GANGLIA

General Morphology of Ganglion Cells.—The autonomic ganglion cells are multipolar neurons with variable numbers of dendritic processes. In general they are aggregated in ganglia which are more or less definitely delimited and enclosed in connective tissue capsules. In all the larger ganglia the perikaryon, or cell body, of every ganglion cell is enclosed in a delicate cell capsule which is penetrated by all the longer dendrites.

The autonomic ganglion cells vary in form and size within relatively wide limits. In mammals, including man, the cell bodies of some of these neurons are oval in outline, those of others are pyriform, globose or polygonal. In some instances the form of the cell body depends on the character of the larger cytoplasmic processes, in others it is modified by its relationships to adjacent neurons or other tissue elements. The autonomic ganglion cells naturally fall into three categories on the basis of the volumes of their cell bodies: large, medium sized and small. In man the maximum diameters of the large ganglion cells vary from 35 to 55 or even 60 microns, those of the medium sized ones from 25 to 34 microns, and those of the small ones from 15 to 24 microns (de Castro, 1932). The ganglia are not all comparable with respect to the sizes of their constituent ganglion cells. The cells of the several volume categories also vary in proportion to those of the other categories in different ganglia. According to de Castro, the largest of all autonomic ganglion cells occur in the superior and middle cervical sympathetic trunk ganglia. Ganglion cells of medium sizes predominate in most of the autonomic ganglia except those of the sympathetic trunk. In the latter, large and small ganglion cells occur in approximately equal numbers, except in the superior cervical ganglion in which large ones predominate. In the prevertebral ganglia, the ganglion cells exhibit greater uniformity in volume. The maximum diameters of most of these cells fall within a range of 35 to 42 microns. The greatest cytometric variations undoubtedly occur in the ganglia which are most complex structurally and functionally.

All the cytoplasmic processes of a ganglion cell except one, which represents the axon, may be regarded as dendrites. The length of the axon is determined by the anatomical relationships of the neuron, but whether it be short or relatively long it represents but a relatively small percentage of the cytoplasm of the neuron. The dendrites vary in numbers, lengths and calibers within relatively wide limits. They may therefore represent a relatively large percentage of the cytoplasm of the neuron or only a small portion of it.

Cytological Structure.—**Neurofibrils.**—Neurofibrils are constant constituents of autonomic ganglion cells. They are present throughout the cytoplasm, including the axon and dendrites (Fig. 9), but vary within a wide range in abundance, distribution and arrangement. Preparations of ganglia in which the neurofibrils are abundant in most of the ganglion cells, and well stained, reveal some cells in which these structures may be

observed only in the cytoplasmic processes and the peripheral zone of the cell body, but not in the perinuclear zone. In such cells the neurofibrils appear more delicate than in those in which the neurofibrillar structure is more abundant. In many ganglion cells the neurofibrils seem to run singly or in small bundles through the cell body in various directions; in others they appear to interlace with one another, the deeper fibrils forming a perinuclear plexus. The neurofibrils in the deeper portion of the cytoplasm appear to be arranged with reference to the nucleus, those in the superficial portion with reference to the periphery of the cell body and the dendrites. In many ganglion cells the deep and superficial complexes of neurofibrils are quite distinct but not independent of one another. Cajal (1905) recognized these two neurofibrillar configurations and described a peripheral and a perinuclear neurofibrillar network. Laignel-Lavastine (1906) and Michailow (1908) also recognized these neurofibrillar arrange-

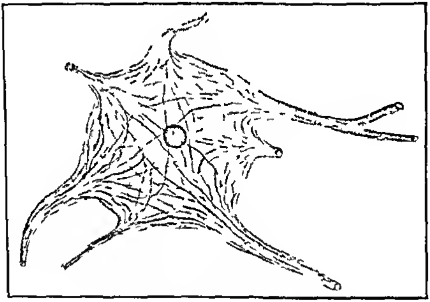

Fig. 9.—Sympathetic ganglion cell (human) drawn from a pyridine silver preparation to illustrate the neurofibrillar structure.

ments. In preparations in which the neurofibrillar structure is well differentiated, neurofibrils lying parallel to one another may be observed in the axons and dendrites throughout the greater part of the length of these processes. Not infrequently individual neurofibrils may be traced from the axon or a dendrite into the cell body where they take part in some particular configuration pattern. Individual neurofibrils may only rarely, if ever, be traced from one cell process into another through the cell body.

The exact nature of the neurofibrils as yet is unknown. Since they have been demonstrated in living neurons (Bozler, 1927) they may not be regarded as artifacts. They are not homogeneous but possess a central core which is less rigid than the peripheral layer. They probably are functionally related to intracellular metabolism (Parker, 1929) but the evidence on which this hypothesis is based cannot be regarded as conclusive. Not infrequently ganglion cells exhibit hypertrophy of the neurofibrils which probably has pathological significance (Michailow, 1908).

Chromidial Substance — Autonomic ganglion cells, like other neurons, possess chromidial substance (Fig 10) This substance appears relatively early and is fairly abundant in most of the autonomic ganglion cells in man before birth In the newborn the autonomic ganglion cells exhibit approximately the same range of variation in the sizes of the chromidial bodies and in their distribution as in the adult (Spiegel and Adolf, 1922)

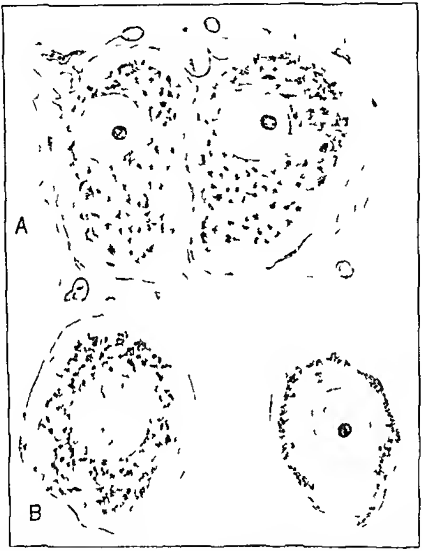

Fig 10 —Sympathetic ganglion cells (cat) *A* Selected to illustrate normal distribution of chromidial substance in resting cells *B* Selected to illustrate variations in the distribution of the chromidial substance

According to Ping (1921), who studied the development and distribution of the chromidial bodies in the largest cells in the superior cervical sympathetic ganglion of the albino rat from birth to maturity, these cells exhibit progressive changes in the quantity of the chromidial substance and in the character and distribution of the chromidial bodies During the first twenty days of postnatal life, the chromidial substance is fairly uniformly distributed throughout the cytoplasm and the chromidial bodies are relatively small but before the close of this period, a beginning of aggregation of the chromidial granules is apparent in some of the cells The chromidial bodies in the cells in question later become larger and stain more intensely Before the sixtieth day of postnatal life, the chromidial sub-

stance in the majority of these cells is aggregated either in the peripheral or the perinuclear zone Many of them also exhibit the same modes of distribution of the chromidial substance following this period In view of the effect of cellular activity on the abundance and distribution of the chromidial substance in ganglion cells it is not improbable that the variations which Ping described as correlated with age may be expressions of the metabolic states of the cells and only indirectly dependent on age

In the autonomic ganglion cells the chromidial substance is affected by cell activity and fatigue in essentially the same manner as in the neurons in the cerebrospinal nervous system Vas (1892) observed enlargement of the cells and displacement of the chromidial substance toward the periphery in the cervical sympathetic ganglia following stimulation for fifteen minutes Lambert (1893) observed similar aggregation of the chromidial substance in the peripheral zone following stimulation, but no changes in the sizes of the ganglion cells Mann (1894) observed enlargement of autonomic ganglion cells during cell activity, and shrinking of both nucleus and cytoplasm as the cells become fatigued He also maintained that the chromidial bodies become enlarged during moderate cell activity, but prolonged stimulation results in diminution in the quantity of the chromidial substance Lugaro (1895) also reported an initial enlargement of both the cell bodies and the nuclei of autonomic ganglion cells due to cell activity According to his observations, if these cells are subjected to prolonged stimulation, the enlargement of the cell body reaches its maximum in five minutes and that of the nucleus in thirty minutes After this both the cell body and the nucleus undergo diminution in size, rapidly during the first few hours, and then more slowly He also maintained that the chromidial substance was increased during the early phases and diminished during the later phases of cell activity As the cells became fatigued they also exhibited a more diffuse distribution of the chromidial substance Section of the preganglionic fibers to the superior cervical sympathetic ganglion (cat rabbit), according to Sternschein (1923), resulted in changes in the chromidial substance and diminution in the size of the neurons in this ganglion The chromidial bodies became larger and more compactly aggregated and assumed a somewhat fibrous appearance They also reacted more intensely to basic stains The progressive changes in the chromidial content of the autonomic ganglion cells during stimulation have been studied systematically by Bradshaw[1] (1930) and Ingersoll (1932) Their results clearly demonstrate that chromidial substance is consumed during cell activity and that the ganglion cell at first responds by increased production of this substance If stimulation is long continued the rate at which the chromidial substance is produced falls below that at which it is consumed and the supply becomes depleted In general, the changes described by Bradshaw and Ingersoll are comparable to the progressive changes in the chromidial substance described by Dolley (see Chapter XVIII) in certain neurons in the central nervous system, particularly the Purkinje cells in the cerebellum, during stimulation

Pigment —The occurrence of pigment in autonomic ganglion cells is of peculiar interest in relation to intracellular metabolism The presence of pigment in the ganglion cells of the sympathetic trunk and the prevertebral plexuses in human fetuses of six or seven months has been reported (de

[1] Unpublished data

Castro, 1923) Its presence in the newborn and during the early years of life has been observed by various investigators (Lubimoff, 1874, Vass, 1892, Pilz, 1895, Spiegel and Adolf, 1922)

The pigment observed in the autonomic ganglion cells, like that in other parts of the nervous system is of two kinds (*a*) yellow lipoid pigment which is soluble in alcohol, ether and other fat solvents and reacts to fat stains, and (*b*) dark melanotic pigment which is highly insoluble The lipoid pigment arises earlier than the melanotic pigment but is rarely observed in sections of autonomic ganglia unless fat solvents have been avoided in their preparation Melanotic pigment is rarely present in abundance in the autonomic ganglion cells in the young except in association with pathological processes According to Spiegel and Adolf (1922) and Herzog (1931), the two kinds of pigment represent diverse but independent stages in products resulting from intracellular metabolism The lipoid and melanotic pigments probably are not genetically related to one another, but represent well-defined morphological entities both in their origin and from the standpoint of their chemical nature (de Castro, 1932) Melanotic pigment is relatively scarce in the ganglion cells of small mammals but abounds in those of the ruminants and various other larger mammals, including the primates (de Castro, 1923 1926)

Nucleus — The nuclei in the autonomic ganglion cells are similar in appearance to the nuclei in the neurons in the central nervous system They usually are relatively large, rounded or oval in outline and contain relatively little stainable material except one or more nucleoli In most of the cells the nucleus is centrally located but in many it occupies an eccentric position In favorable preparations, the nucleus exhibits a reticular structure and is separated from the cytoplasm by a distinct nuclear membrane

In man the autonomic ganglion cells, with few exceptions, are uninucleated Binucleated ganglion cells, according to Spiegel and Adolf (1920), are not uncommon in the autonomic ganglia in young persons They also reported the occurrence of multinucleated autonomic ganglion cells in the newborn According to their findings in human material, the binucleated ganglion cells diminish in number with advancing age The observation that binucleated ganglion cells occur quite commonly in the autonomic ganglia in young persons, but only rarely in the aged, led Spiegel and Adolf to advance the opinion that these cells retain the capacity to undergo division without further nuclear changes and that such division occurs even during adult life De Castro (1923) also regarded the binucleated autonomic ganglion cells as reserve cells which may still undergo division The occasional occurrence of two ganglion cells in a common cell capsule lends support to this theory In certain mammals, particularly rodents, binucleated autonomic ganglion cells occur in relatively large numbers (Marinesco, 1898, Spiegel and Adolf, 1921, de Castro, 1923)

Nucleus plasma Ratio — By careful measurements, Spiegel and Adolf (1922) found that the nuclei of the larger ganglion cells in the autonomic ganglia in man have diameters of 12 to 13 microns, while those of the smaller ones have diameters of 8 to 12 microns In young children, according to their observations, the nuclei of the autonomic ganglion cells are nearly uniform in size regardless of the sizes of the cell bodies Those of the smaller ganglion cells are larger in proportion to the size of the cell body

than those of the larger ones. The nucleus apparently increases in volume less rapidly than the cytoplasm during the growth of the cells. According to Ping (1921), the nucleus plasma ratio of the ganglion cells in the superior cervical ganglion is 1 to 4 in the albino rat and 1 to 5 in the Norway rat at birth, and 1 to 12 in both varieties at maturity.

The nucleus plasma ratio probably is fairly constant in mature autonomic ganglion cells of approximately uniform size. When all the neurons in a given ganglion are considered it seems to vary within relatively wide limits. These cells apparently do not conform closely to Hertwig's law of the constancy of the nucleus plasma ratio. Heidenhain (1907) expressed the opinion that this may be related to the capacity of the neuroblasts to produce short or long axons according to their location and relationships to the tissues innervated by them. In view of the apparent inconstancy of the nucleus plasma ratio in the autonomic ganglion cells the quantity of chromidial substance present in the cytoplasm is relatively unimportant. This substance being histochemically related to the chromatin in the nucleus, as Heidenhain suggested, probably is present in relatively greater quantity in the larger than in the smaller cells particularly if the larger ones have long axons. He therefore expressed the opinion that the nucleus plasma ratio might still be regarded as constant on this basis.

Axon.—The axon of the autonomic ganglion cell commonly arises from an implantation cone or axon hillock which, as in the neurons in the central nervous system, is free from chromidial substance but is less conspicuous in the former cells than in the latter. Neurofibrils may be traced through the implantation cone into the axon where they lie closely aggregated and parallel to one another. In most instances the axon is a slender unmyelinated fiber but ganglion cells with myelinated axons are not uncommon. Autonomic fibers with very thin myelin sheaths throughout at least a portion of their length probably occur throughout the autonomic nervous system.[1] The nucleated neurilemma of the unmyelinated autonomic fibers lies in intimate contact with it. Even in the cases of those fibers which are covered by a thin layer of myelin, the neurilemma invests the axon so closely that nodes and incisures usually are not apparent. In mammals the axons of autonomic ganglion cells rarely are myelinated throughout their entire length. Those which are invested by myelin acquire their myelin sheaths at unequal distances from their origin. Myelinated autonomic fibers are more abundant in proportion to the unmyelinated ones in some parts of the body than in others. The ratio of myelinated to unmyelinated autonomic fibers also varies in the different classes of vertebrates and in different species in the same class. The sympathetic fibers which join the spinal nerves via the gray communicating rami, particularly in mammals, probably are myelinated in greater proportion than those which supply the visceral organs, although myelinated fibers also exist among those arising from the prevertebral sympathetic ganglia. According to Huber (1913), the axons of the neurons in the ciliary ganglion quite generally are myelinated. In birds, according to Langley (1896),

[1] Diamare and Menusto (1931), by the use of polarized light, claim to have demonstrated myelin sheaths on autonomic axons of all calibers, even the smallest, although the myelin investing the smaller fibers is exceedingly thin. They have proposed the use of the terms "myelin rich" and "myelin poor" as more appropriate than the terms myelinated and unmyelinated, respectively.

true gray communicating rami do not occur, but the axons of all the neurons in the ganglia of the sympathetic trunks are myelinated Myelinated autonomic nerve fibers also have been described in the Amphibia Most of the accounts of the autonomic nerves in fishes and reptiles refer only to unmyelinated fibers The data available at present warrant no conclusion regarding the significance of myelin sheaths in the autonomic nervous system Neither do they indicate that the myelinated autonomic fibers differ functionally from those devoid of myelin

Autonomic End formations and the Neuron Theory —The axons of autonomic ganglion cells which terminate in relation to smooth muscle commonly form delicate plexuses around individual muscle fibers or groups of fibers Hoffman (1907) advanced the opinion that the terminal neural structure in smooth muscle is a plexus composed of fibrils which give rise to loops which lie in relation to muscle cells but the fibrils go on without interruption Michailow (1908) also supported the theory of a terminal plexus but described free terminations which, in favorable preparations, show ring like and net-like fibrillar structures The axons which terminate in relation to gland cells, according to most observers, form a plexus adjacent to the membrana propria, from which arise fibers which penetrate the membrana and terminate in relation to the gland cells

The results of extensive painstaking histological studies in which attention has been focussed on the terminal nervous structure in the tissues innervated through the autonomic nerves and the so-called interstitial cells associated with the enteric plexuses have raised pertinent questions regarding the validity of the neuron theory These questions have been discussed extensively particularly by Boeke (1940)

Terminal structures in smooth muscle have repeatedly been described as end-rings or end-nets, but many investigators using the specialized methylene blue and silver technics have been impressed with the difficulty of obtaining preparations in which terminal structures of this kind can be demonstrated Preparations in which the nerve fiber bundles are successfully impregnated not infrequently fail to reveal free terminal structures but show well impregnated fibrillar networks, in intimate relationships with smooth muscles and glands which have been variously interpreted as nerve and as connective tissue

Stoehr, Jr (1932, 1935) and Reiser (1932, 1933) have described a delicate fibrillar structure, the "terminal reticulum," in autonomically innervated tissues which they regard as continuous with the axons of autonomic ganglion cells and with the protoplasm of the innervated tissue elements As described and illustrated by them this structure resembles a meshwork of connective tissue fibers Since certain connective tissue elements may be impregnated in silver preparations or stained with methylene blue certain investigators, particularly Nonidez (1936, 1937), have been unable to accept the conclusions of Stoehr and Reiser regarding the relationships of the so-called terminal reticulum to the autonomic nerves but regard it as a connective tissue structure without continuity with the nerves

In an extensive series of studies Boeke (1933–1936) has described a fibrillar structure associated with the autonomic nerves which he has called the "ground plexus" This structure which consists of unmyelinated nerve fibers arranged in strands or flattened bands of very delicate neurofibrils is present throughout the body It is commonly associated with the

smaller blood vessels, including the capillaries, and is intimately related to smooth muscle and gland cells Nuclei which have been regarded as those of neurilemma cells occur dispersed between the neurofibrils The ground plexus, according to Boeke, appears to extend to the muscle cells and may be traced into their cytoplasm as an exceedingly delicate network which is lost in the longitudinal striation of the myofibrils He regards this structure as the mechanism through which impulses conducted through the autonomic nerves reach the effector organs If, as Boeke contends, the ground plexus is a syncytial structure which is continuous with the axons of autonomic ganglion cells, the latter can hardly be regarded as discontinuous in the sense of the classical neuron theory

The so called interstitial cells of Cajal, which are particularly abundant in the wall of the gastro intestinal canal, are closely associated with the autonomic nerves These cells have been variously interpreted as nerve cells and as connective tissue elements, but, throughout his scientific career Cajal regarded them as primitive neurons Lawrentjew (1929-1934) regarded them as the important elements in the end formations of the autonomic plexuses According to his interpretation the most delicate branches of the autonomic plexuses exhibit a syncytial structure in which the neurofibrillar strands are enclosed in protoplasmic sheaths which exhibit no definite cell membranes but have neurilemma nuclei associated with them As such strands are traced between the tissue elements, a protoplasmic body enclosing a nucleus is encountered at intervals along their courses These are the so-called interstitial cells Their processes are irregular and anastomose freely with those of adjacent interstitial cells Bundles of fibrils consequently may be traced from one of these cells into an adjacent one This point of view has been supported by Leontowitsch (1930) Schabadasch (1934) and others who regard the interstitial cells as a portion of the autonomic end-formation from which the so-called periterminal network grows out through which nerve impulses are transmitted to the effector organs Li (1940) found interstitial cells particularly abundant in the inner layer of the circular muscle in the small intestine He advanced the hypothesis that this layer represents a neuromuscular mechanism which probably bears a definite relationship to irritability, conduction and rhythmic contractions and consequently, plays a major role in the ordinary activities of the gastro-intestinal tract in the absence of regulatory control through the extrinsic nerves

If the anatomical structure through which the autonomic nerves are functionally related to the effector organs is a syncytium which actually invades the protoplasm of the tissue elements, as Boeke maintains, the axons of the autonomic ganglion cells cannot be regarded as separated from the effector cells by a limiting membrane as required by the classical neuron theory If the so called interstitial cells, furthermore, are primitive neurons which are syncytially connected with one another and with the axons of ganglion cells, it cannot be maintained that all neurons are morphologically independent units separated from one another by surface limiting membranes Although the results of careful histological studies carried out by certain investigators of undoubted ability fail to support the assumption that either the ground plexus or the so-called interstitial cells are of nervous origin it must be conceded particularly in view of the doctrine of the chemical mediation of nerve impulses, that a formation

such as the ground plexus described by Boeke, which affords relatively large areas of junctional tissue, seems to meet the physiological requirements for the transmission of nerve impulses more completely than minute free terminal structures lying here and there on the surface of the effector elements or an indifferent terminal reticulum which surrounds them

The neuron theory has played a more important role in the advancement of neurology than the doctrine of the continuity of nerve cells The physiologic concept of the synapse undoubtedly is valid The neuron theory in its classical form obviously does not take adequate account of the more modern concepts of the minute structure of the organism and the arrangement of its nerves It should therefore be modified but not abandoned Even though the structure through which impulses are transmitted from the autonomic axons to the effector cells should have to be regarded as syncytial, a synaptic arrangement of autonomic neurons would still remain necessary

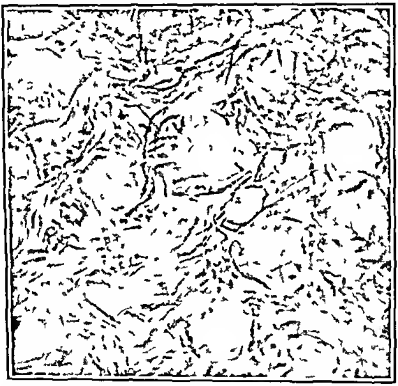

FIG 11 —Photomicrograph from a section of a celiac ganglion (human) prepared by a modification of Cajal's silver technic

Dendrites —The autonomic ganglion cells vary within wide limits in the numbers and the morphological characters of their dendrites These processes may be broad at the base and taper distalward or they may be of nearly uniform diameter throughout the greater part of their lengths They commonly give rise to branches and frequently exhibit varicosities and other irregularities They also include neurofibrils which in favorable preparations, may be traced into their terminal branches The broader proximal portions also include chromidial bodies Many of the short dendrites lie wholly within the ganglion cell capsule The longer ones usually penetrate the ganglion cell capsule and ramify more or less widely within the ganglion (Fig 11) In some instances long dendrites extend beyond the border of the ganglion in fiber bundles associated with it

Two ganglion cells joined together by a cytoplasmic bridge have been observed particularly in the myenteric plexus (Cole, 1921, Waddell, 1928) In most instances the cells joined in this manner lie close together, in some they are removed from one another by a distance equal to several times the diameter of a ganglion cell body Anastomosing ganglion cells probably are relatively uncommon Cole (1921) advanced the opinion that they belong to the same category as binucleated ganglion cells but the data on which this opinion is based cannot be regarded as conclusive

Classification of Ganglion Cells.—The morphological characters and the distribution of the dendrites have been used as criteria for classification of the autonomic ganglion cells In his early studies Dogiel (1896 1899) described ganglion cells of three morphological types which he regarded as distinct from one another According to his account based mainly on preparations of the cardiac and the enteric ganglia, the ganglion cells of type I have a long axon and short dendrites which branch freely in the vicinity of the cell body, those of type II are characterized by long branching dendrites many of which in the enteric canal terminate in relation to the mucous epithelium, and an axon which arborizes within the ganglion those of type III have dendrites of medium length which arborize around cells in the same ganglion or an adjacent one, and a long axone Cajal (1905) also recognized ganglion cells of three morphological types His descriptions of these cells are based mainly on preparations of the superior cervical ganglion in man Those of type I have short intracapsular and glomerular dendrites, those of type II have long dendrites and those of type III have both short and long dendrites Ganglion cells of types I and III occur relatively infrequently in the animals most commonly used in the laboratory (cat, dog, rabbit) but in greater abundance in the larger mammals and more particularly in the primates (de Castro 1923 1926) The short intracapsular dendrites commonly terminate within the wall of the ganglion cell capsule, sometimes they form a crown or a nest around the ganglion cell body, and in some instances a glomerular structure within the ganglion cell capsule The long dendrites are less numerous than the short ones They penetrate the ganglion cell capsule and become arranged in dendritic tracts or fasciculi glomerular plexuses and dendritic crowns and pericellular dendritic nests Cajal's classification has been accepted by various investigators, including Marinesco (1906), Muller (1909), Terni (1922), de Castro (1923) and others

De Castro (1932) adopted a classification of autonomic ganglion cells which differs somewhat from that of Cajal outlined above It also is based on the morphological characters of the dendrites but takes into consideration their distribution and their relationships to adjacent ganglion cells

Type I Cells with Primordial or Long Dendrites.—Ganglion cells of this type vary in sizes and forms but their dendrites are mainly long processes which may arise from all parts of the cell body or from limited areas of its surface In man and other large mammals during adult life, some of the dendrites of these cells branch only sparingly and are of approximately uniform thickness throughout the greater part of their length, others give rise to many branches some of which remain relatively short Dendrites with thickenings from which branches arise which have greater diameters than the main stem are not uncommon Fenestrated dendrites also occur

In the primates including man the autonomic ganglion cells are mainly of the long dendritic type during late fetal life and childhood The condition of the dendrites which obtains in adult life is attained by a gradual process in which the most conspicuous changes take place from the sixth or eighth to the twenty-fifth year During adult life, ganglion cells with long dendrites abound in the sympathetic trunk ganglia and are most numerous in the prevertebral ganglia In their mature condition many of the ganglion cells with long dendrites also have shorter, accessory dendrites Many dendrites exhibit 'collateral twigs' which are either simple or sparsely branched These twigs according to de Castro (1923), constitute receptive mechanisms, the so-called "receptor plates and collateral glomeruli"

Throughout the autonomic nervous system the terminal arborizations of the long dendrites and their collateral twigs are arranged in characteristic configurations in definite areas of the ganglia Not uncommonly the terminal branches of dendrites arborize around the cell bodies of other ganglion cells, forming the so-called pericellular dendritic nests of Cajal (Fig 12) These are not accidental arrangements but mechanisms through which the dendrites in question effect synaptic contacts with preganglionic fibers whose terminal branches arborize around the same ganglion cell bodies (Cajal, 1906, de Castro, 1923)

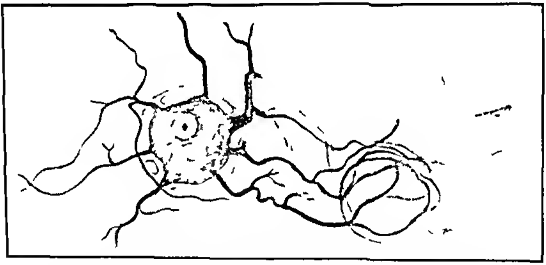

FIG 12 —Drawing from a preparation of a sympathetic ganglion (human) illustrating arborization of dendrites around the body of an adjacent ganglion cell

In some instances the terminal branches of long dendrites ramify among those of one or more ganglion cells with shorter dendrites the terminal branches of which form a glomerular structure which may be enclosed in a common capsule This probably is not a common arrangement Cajal (1906) described it in the superior cervical ganglion in man De Castro (1923) also recognized it in other ganglia of the sympathetic trunk

Most of the long dendrites are arranged in fasciculi or tracts of various sizes, the protoplasmic tracts of de Castro (Fig 13) Dendrites of numerous ganglion cells are intimately associated with one another in such tracts Cajal (1906) observed that many dendrites terminate by means of olive-shaped enlargements in the protoplasmic tracts According to de Castro (1932), some protoplasmic tracts traverse a ganglion without receiving

dendritic terminations, others receive such terminals in large numbers The latter appear as triangular or olive-shaped swellings bearing small divergent processes articulated with preganglionic fibers

The most common mode of termination of the dendrites of autonomic ganglion cells, according to de Castro, is that which he has designated the "receptor plate" Such a structure involves terminal arborizations of some dendrites and short collateral twigs of others All the dendrites involved in such a formation probably receive impulses conducted by the same preganglionic axons

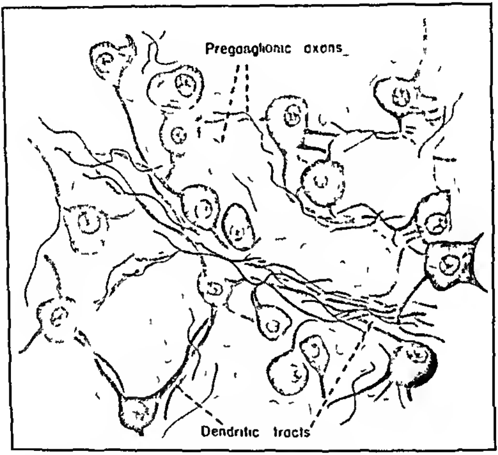

FIG 13 —Drawing from a section of a celiac ganglion (human) prepared by a modification of Cajal s silver technic to illustrate arrangement of long dendrites in fasciculi or tracts

Type II Monocellular and Pluricellular Dendritic Glomeruli —Cajal (1906) described glomerular structures in the superior cervical sympathetic ganglion in man consisting of one two or more neurons which in some instances are enclosed in a common connective tissue capsule This arrangement of ganglion cells has been described in greater detail by de Castro (1923 1932) A glomerulus which involves but a single ganglion cell is a relatively simple structure Most of the dendrites arise from the cell body in a limited area They are mainly short processes which give rise to numerous branches which form a glomerular plexus near the cell body If a glomerulus consists of two ganglion cells most of the dendrites of each are directed toward the other, their branches forming a glomerular plexus between the two cell bodies If several ganglion cells are involved in a glomerulus

they usually are arranged at the periphery of the group (Fig 14) Most of the dendrites of these cells are directed toward the center of the group where they form a glomerular plexus In larger glomeruli ganglion cell bodies also appear in the central area Not all the dendrites which become involved in a glomerulus terminate within it Some emerge from it and enter a protoplasmic tract or another glomerulus Glomeruli also receive long dendrites of ganglion cells which are not incorporated in it Dendrites of a ganglion cell incorporated in a glomerulus which do not enter the general glomerular plexus may terminate in pericellular nests around the cell bodies of adjacent ganglion cells within the same glomerulus or in small accessory glomeruli involving one or more dendrites of adjacent ganglion cells Glomerular arrangements of ganglion cells according to de Castro (1923) are less common in the smaller mammals than in the larger ones, including man

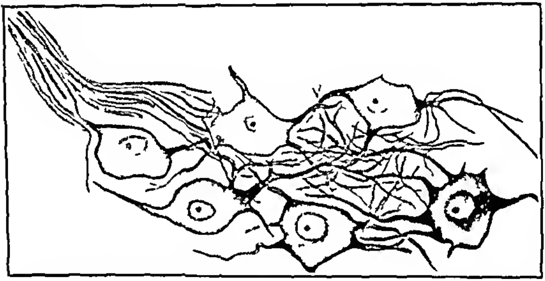

FIG 14 —Drawing from a preparation of a celiac ganglion (human) showing ganglion cells in glomerular arrangement Dark fibers represent preganglionic axons (Kuntz 1938 courtesy of Jour Comp Neurol)

From the functional point of view, according to de Castro (1932), a glomerulus may be regarded as an intraganglionic nucleus made up of neurons which are isodynamically associated with one another, all of which receive impulses through the preganglionic fibers which terminate in it Glomeruli arise early in embryonic development and persist throughout life, becoming more complex with advancing age

Type III Cells with Short or Accessory Dendrites —This category includes ganglion cells with only short dendrites and ganglion cells with short and long dendrites In the human fetus and the very young infant, according to de Castro (1932), the short dendrites under discussion either are absent or present in very small numbers They arise during postfetal life and develop slowly (Terni, 1922, de Castro, 1923) Many ganglion cells which at first have only long dendrites gradually develop short ones The budding and growth of accessory dendrites takes place mainly from the eighth to the fourteenth year Short processes which were already present also increase in thickness and may give rise to branches during this period

Many of the accessory dendrites do not penetrate the ganglion cell

capsule (Fig 15) They may be thick or thin Some are unbranched others give rise to few or a larger number of branches which end in small knobs or spherical enlargements of variable sizes Some terminal branches exhibit tuberosities or bead like structures Still others taper to a sharp point Ganglion cells with short dendrites are less common in the smaller mammals than in the larger ones, including man

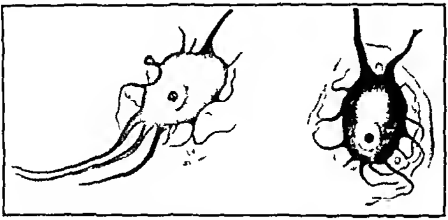

Fig 15 —Sympathetic ganglion cells (human) with long and short (accessory) dendrites The short dendrites are mainly intracapsular

Type IV Fenestrated Ganglion Cells —Fenestrated ganglion cells occur in small numbers particularly in the cephalic autonomic ganglia of man and other large mammals In some cases the fenestrations appear as simple tracts resembling cup-handles or as fibers which anastomose with one another near their origin, in others they are more elaborate and involve stout dendritic branches which anastomose repeatedly Ganglion cells with perforations in the peripheral zone of the cell body also have been observed

Type V Small Ganglion Cells —Some of the small ganglion cells, particularly in the sympathetic trunk ganglia, retain the general appearance of young cells throughout life They do not attain the degree of differentiation reached by the other ganglion cells and fall within a range of 15 to 24 microns in maximum diameter The cell bodies may be ovoid or pyriform and possess few dendrites nearly all of which are long but only of moderate length Although fairly numerous in the sympathetic trunk ganglia, cells of this type occur only rarely in the celiac and mesenteric ganglia

Structural Characteristics of Autonomic Ganglia —The autonomic ganglia vary within a wide range in form, size and the number of their constituent ganglion cells In general every ganglion is enclosed in a connective tissue capsule and exhibits a connective tissue framework which, in sections of most of the ganglia, is relatively inconspicuous The interstitial connective tissue is continuous with the connective tissue capsule It is present throughout the ganglion and the intraganglionic blood vessels are imbedded in it Slit like lymph spaces connected with the lymph channels in the ganglion occur in proximity to the ganglion cell capsules The relationships of these spaces to the latter suggests that the endothelial-like cells lining the capsules play an *important* role in the metabolic interchange of materials and degenerative processes involving the ganglion

cells The smaller terminal ganglia, e.g., those in the wall of the enteric canal, are less sharply delimited. They are surrounded by connective tissue but a clearly defined capsule is not apparent in all cases.

Among the conspicuous structural features in sections of a ganglion are the nerve fibers which enter it and those which arise from its constituent ganglion cells. The bundles of nerve fibers which enter a ganglion pursue more or less regular courses in some instances but exhibit no regular arrangement in others. These bundles consist mainly of preganglionic fibers which terminate in the ganglion and preganglionic and afferent fibers which traverse it. In general the long dendrites of the ganglion cells are arranged in dendritic tracts or fasciculi. Some of the short dendrites become associated with these tracts, particularly through their terminal branches, others give rise to glomerular structures in which dendrites of two or more adjacent ganglion cells intertwine with one another. In sections, groups of ganglion cells with long dendrites not uncommonly appear to be separated from one another by the dendritic tracts. Ganglion cells whose dendrites intertwine in dendritic glomeruli constitute more or less definitely circumscribed glomerular groups (Fig. 14). Ganglion cells with both long and short dendrites may be associated with adjacent neurons both through dendritic tracts and dendritic glomeruli.

Most of the autonomic ganglia include ganglion cells of diverse morphological types but some exhibit greater diversity than others in this respect. The superior cervical sympathetic ganglion includes ganglion cells which differ widely in their morphological characters, including size. Most of them have both long and short dendrites. Ganglion cell glomeruli are not uncommon. They comprise one or more ganglion cells and may be regarded as small isodynamic ganglion cell centers. Ganglion cells of large and medium sizes, some of the dendrites of which end in dendritic plexuses which are less highly differentiated than the dendritic glomeruli, also are characteristic of this ganglion. Many of the long dendrites present are arranged in stout dendritic tracts in which receptor plates occur only in limited areas. Most of the short dendrites do not penetrate the ganglion cell capsule. These, according to de Castro (1932), probably represent specific receptors differentiated for the purpose of receiving individualized nerve impulses. The stellate ganglion exhibits certain structural characteristics in common with the other sympathetic trunk ganglia and others in common with the prevertebral ganglia. The thoracic sympathetic trunk ganglia exhibit greater uniformity with respect to the morphological characters of their constituent ganglion cells. Slender dendritic tracts are common but there are few pluricellular glomeruli. Most of the ganglion cells have both long and short dendrites. Many of the latter do not extend beyond the ganglion cell capsules, others penetrate the capsule and terminate in receptor plates near by. The lumbar and sacral sympathetic ganglia also exhibit uniformity with respect to the morphological characters of their constituent ganglion cells in a relatively high degree. Most of these cells have both long and short dendrites. The long ones lie mainly in dendritic tracts. Most of the short ones are relatively straight. They penetrate the ganglion cell capsule and terminate in arborizations outside the capsule. In some instances their terminal branches interlace with those of similar dendrites of adjacent ganglion cells to form dendritic "brushes" and accessory glomeruli.

The prevertebral ganglia are characterized by ganglion cells of medium sizes and a high degree of uniformity in their morphological characters. They are mainly stellate cells with long dendrites. Very small and very large ganglion cells occur only rarely in these ganglia. In addition to the long dendrites, many of the cells have short accessory dendrites, which

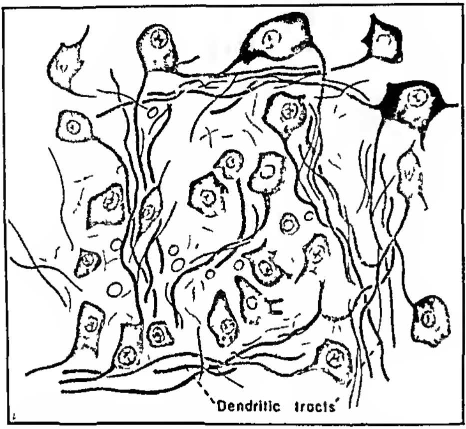

FIG 16 —Drawing from a section of a sympathetic ganglion of a newborn child showing a group of ganglion cells delimited by slender dendritic tracts. The dark fibers represent preganglionic axons

penetrate the ganglion cell capsule and invade the dendritic tracts or, with short dendrites of adjacent cells, form dendritic brushes and accessory dendritic glomeruli. A striking feature in sections of these ganglia is the occurrence of extensive groups of ganglion cells surrounded by slender dendritic tracts (Fig 16). Isolated ganglion cells surrounded by connective tissue occur only rarely.

The cranial autonomic ganglia comprise mainly ganglion cells of medium sizes but include large ones in appreciable numbers and few small ones. Most of these cells have both long and short dendrites. The long ones give rise to relatively few branches, most of which are short and terminate in bulbous or club-shaped enlargements. Many of the short ones do not extend beyond the ganglion cell capsule. Not infrequently the axon arises from the proximal portion of a dendrite.

The visceral ganglia, particularly those in the enteric canal, comprise mainly ganglion cells of two or three morphological types. In the myenteric and submucous ganglia, Dogiel (1899) described cells with short dendrites (Type I), cells with long dendrites (Type II) and cells with dendrites of

intermediate lengths (Type III) Most investigators who have studied these ganglia have recognized ganglion cells corresponding to those of type I and type II of Dogiel but some do not recognize the need of a third category for cells with dendrites of intermediate lengths, since both those of type I and type II exhibit wide variations in the lengths of their dendrites In general the short dendrites of the cells of type I give rise to numerous short branches, whereas the long dendrites of the cells of type II branch only sparingly Not infrequently the short dendrites of contiguous ganglion cells form dendritic brushes or glomeruli Terminal branches of long dendrites of cells of type II in some instances also end in these structures Not infrequently long dendrites terminate in pericellular dendritic nests in the same ganglion or in an adjacent one

Nerve Fibers in Autonomic Ganglia — The nerve fibers present in autonomic ganglia include the axons of the autonomic ganglion cells preganglionic axons which effect synaptic connections in the ganglia and afferent cerebrospinal nerve components which traverse them The axons of the ganglion cells commonly emerge from the ganglia and join the nerves through which they are conveyed to the effector tissues They have been designated the postganglionic fibers The preganglionic axons arise from visceral efferent neurons in the brain stem and spinal cord and reach the autonomic ganglia via the efferent roots of the corresponding cerebrospinal nerves They constitute the conductors through which impulses emanating from the central nervous system reach the autonomic ganglia The afferent cerebrospinal nerve components merely traverse the autonomic ganglia without effecting functional connections with their constituent ganglion cells

There are no certain criteria on the basis of which the axon of an autonomic ganglion cell may be differentiated from the dendrites in all cases In many instances the axon arises not directly from the cell body but from the proximal portion of a dendrite (de Castro, 1932) It is usually unmyelinated but in some instances it may be sheathed with a very thin layer of myelin Collateral branches occur only rarely if at all (de Castro, 1932) but terminal branches are not uncommon In many instances the axons of the ganglion cells take long tortuous courses through the ganglion before emerging in its gray rami, in others they emerge quite directly

The preganglionic outflow from the central nervous system includes (1) fibers of relatively large caliber with thick myelin sheaths in small numbers, (2) fibers of medium caliber with thinner myelin sheaths in somewhat larger numbers, and (3) fibers of small caliber with thin myelin sheaths in much greater numbers (Langley 1896) Ranson and Billingsley 1918, de Castro, 1927, Stohr, 1927)

Preganglionic fibers of the thoracolumbar outflow terminate in the sympathetic trunk ganglia and the abdominal and pelvic prevertebral ganglia Many of those which effect synaptic connections in the superior and middle cervical ganglia traverse one or more sympathetic trunk ganglia without effecting any connections in the latter Those which reach prevertebral ganglia via the splanchnic nerves also traverse sympathetic trunk ganglia without effecting connections in them Some preganglionic fibers give off terminal branches in one ganglion and continue upward or downward in the sympathetic trunk and give rise to terminal branches in one or more other ganglia Others end in few or many terminal branches

in only one ganglion. The terminal branches of the preganglionic fibers ramify widely within the ganglion. Those of a single fiber may effect synaptic connections with many ganglion cells of identical or similar function but there is no rigid architectural plan or typical localization.

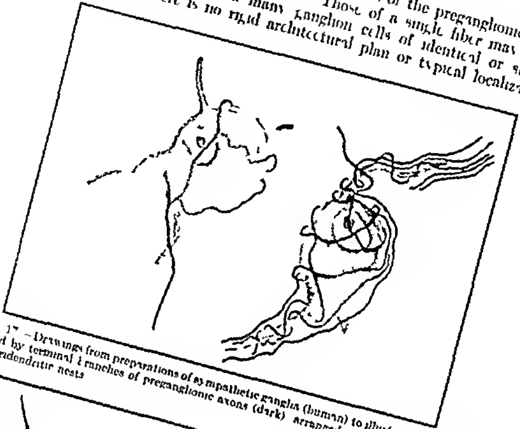

Fig. 17.—Drawings from preparations of sympathetic ganglia (human) to illustrate synapses effected by terminal branches of preganglionic axons (dark) arranged in simple pericellular and peridendritic nests.

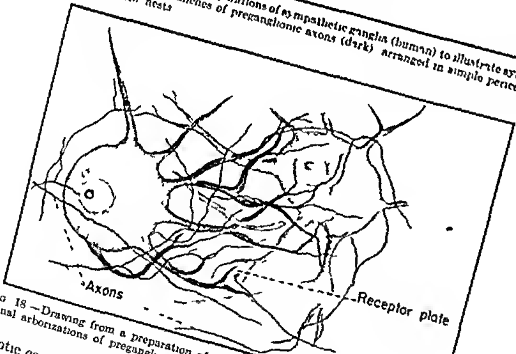

Fig. 18.—Drawing from a preparation of a sympathetic ganglion (human) to illustra terminal arborizations of preganglionic axons in a dendritic glomerulus (Kuntz 1938).

Synaptic connections are established mainly between the terminal arborizations of the preganglionic axons and the receptive structures of the long and short dendrites and of the cell bodies (de Castro 1931). The following types of synaptic mechanisms have been recognized

Pericellular and Peridendritic Nests —One or more preganglionic axons or terminal branches approach a ganglion cell body by spiral courses around dendrites, penetrate the ganglion cell capsule and arborize around the cell forming a more or less complex pericellular nest in contact with the short, accessory dendrites or, in the absence of accessory dendrites in more or less intimate relation to the cell body (Fig 17) The terminal branches typically end in minute rings loops or bulbous enlargements some of which may lie in contact with the surface of the cell body or a dendrite Pericellular fiber terminations of this kind constitute a striking feature of some of our preparations of human ganglia but are less striking in others In some instances only fragments of relatively simple pericellular nests may be observed in sections, in addition to slender darkly stained fibers which approach the cell along one or more dendrites Synapses of this type are less apparent and probably less common in our animal material than in the human

Arborizations in Dendritic Cellular Glomeruli and Dendritic Brushes —In the glomerular complexes formed by the dendrites of adjacent ganglion cells the terminal arborizations of preganglionic axons effect contacts with the dendritic branches (Fig 18) All the ganglion cells involved in such a glomerulus probably are synaptically related to the same preganglionic fibers Axon terminations of the same kind also occur in glomeruli formed by the dendrites of a single ganglion cell and in dendritic brushes formed by dendrites of one or more ganglion cells

Axon Terminations in Dendritic Tracts —In preparations of ganglia in which dendritic tracts are well differentiated the terminal branches of preganglionic axons may be traced among the dendrites Many of these branches terminate in receptor plates (de Castro, 1932) scattered along the tract and at the intersections of bundles of dendrites others probably terminate in relation to the dendrites in the absence of specialized receptor plates (Fig 19) In view of the large percentage of ganglion cells some of the dendrites of which are incorporated in dendritic tracts synaptic connections effected in these tracts must abound in many of the autonomic ganglia

Centripetal Fibers —Many visceral afferent components of the cerebrospinal nerves as stated above traverse autonomic ganglia but effect no connections with their constituent ganglion cells Impulses of visceral origin probably reach the central nervous system only through afferent cerebrospinal nerve components In general reflex responses through autonomic nerves involve afferent conduction into the central nervous system through cerebrospinal nerve fibers and efferent conduction from the central nervous system through pathways consisting of preganglionic neurons and autonomic ganglion cells synaptically related to one another Most of the reflex responses in visceral organs can be explained on this basis, but the autonomous activity of certain viscera, particularly the gastro-intestinal tract, seems to require reflex mechanisms which do not involve centers in the central nervous system

Local enteric reflexes carried out through neurons limited to the myenteric and submucous plexuses have long been recognized on the basis of experimental physiological studies On the basis of anatomical studies, Dogiel (1899) advanced the opinion that the ganglion cells with long dendrites in the enteric ganglia are essentially afferent in function but this

opinion has not been supported by other investigators Anatomical evidence for the existence of synaptic relationships between enteric neurons is not wanting (Kuntz, 1922) but the exact anatomical structure of the enteric reflex arcs as yet is unknown Axons of enteric origin also traverse the mesenteric nerves and effect synaptic connections in the celiac and inferior mesenteric ganglia (Kuntz, 1938, 1940) Reflex responses mediated through the decentralized inferior mesenteric (Kuntz, 1940, Kuntz and Saccomanno, 1944) and celiac (Kuntz and Van Buskirk 1941, Warkentin,

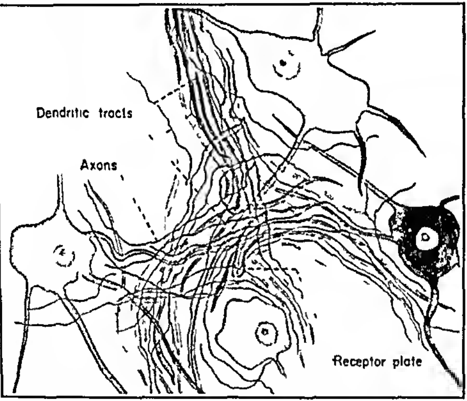

FIG 19 —Drawing from a preparation of a sympathetic ganglion (human) to illustrate relationships of terminal branches of preganglionic axons to dendrites in dendritic tracts (Kuntz 1938 courtesy of Jour Comp Neurol)

Huston, Preston and Ivy, 1943, Kuntz and Saccomanno, 1944) plexuses also have been demonstrated The current teaching that autonomic ganglion cells are essentially efferent in function and constitute the peripheral units in visceral efferent conduction pathways has aided materially in explaining the functional relationships of the autonomic nerves and undoubtedly is correct for the major parts of the autonomic system but exceptions to this point of view must be recognized particularly in the enteric, celiac and mesenteric ganglia

CHAPTER III

CENTRAL AUTONOMIC CENTERS AND CONDUCTION PATHWAYS

Autonomic Nuclei in the Spinal Cord.—The preganglionic fibers of the thoracolumbar autonomic outflow arise mainly from cells in the intermediolateral cell column and in part from cells in the intermediate zone between the anterior and posterior gray columns from the first thoracic to the second lumbar segment inclusive. The extent of the intermediolateral column coincides fairly accurately with that of the thoracolumbar outflow. The preganglionic fibers of the sacral autonomic outflow arise in the intermediate zone, particularly in the nucleus myoleioticus medialis, from the second sacral segment downward. This outflow usually is limited to the third and fourth sacral nerves in man but occasionally some preganglionic fibers are included in the second or the fifth. The central connections of the visceral afferent components of the spinal nerves are not fully known. Like the somatic afferents they effect connections in the posterior gray column and in the intermediate zone of the gray matter, including reflex connections with preganglionic neurons. The latter connections probably involve intercalated neurons.

Certain of the earlier investigators, including Biedl (1895), Hoeber (1896) and Huet (1898), have reported chromatolysis in neurons in the intermediolateral cell column and in certain small neurons in the dorsal part of the ventral gray column in animals following section of the preganglionic fibers in the segments in question. Laignel-Lavastine (1908) reported chromidial changes and atrophy in the nerve cells and reduction in their numbers in these areas and in the paracentral and intermediate zones in the spinal cord of the dog, following extirpation of portions of the sympathetic trunk. Kai (1925) reported marked changes, involving reduction in the number of neurons, chromidial changes and other evidences of nerve cell degeneration in the spinal cord of the dog, following extirpation of portions of the sympathetic trunk. According to his account these changes were well marked ten days after operation. In the upper seven cervical segments the degenerative changes were localized in the dorsolateral region of the ventral gray column and the superficial portion of the intermediate zone. Only a few nerve cells were affected in this portion of the cord. From the eighth cervical to the third lumbar segments, the most marked changes were localized in the intermediolateral cell column. Less marked changes were apparent in the dorsolateral portion of the ventral gray column and the superficial portion of the intermediate zone. Kai regarded the changes described as due to retrograde degeneration, consequently he assumed that the cells affected were visceral efferent neurons.

Gagel (1928) expressed skepticism regarding Kai's findings by calling attention to the difficulties in recognizing early retrograde changes in nerve cells and in the evaluation of apparent differences in the numbers of nerve cells at symmetrical points in sections of the spinal cord. Sections of the normal spinal cord not uncommonly exhibit a high degree of asymmetry in the distribution of nerve cells. In his own studies of the dis-

tribution of visceral neurons in the spinal cord in man Gagel based his conclusions mainly on the morphological characters of the nerve cells In a later study (Gagel, 1931) he reported degenerating neurons in the upper three thoracic segments of the spinal cord ten days after extirpation of the superior cervical sympathetic ganglion

The nerve cells in the intermediolateral cell column differ morphologically from both the somatic efferent neurons in the anterior gray column and the afferent neurons in the posterior gray column Jacobsohn (1908) described the neurons in the intermediolateral cell column in man as club- or bullet shaped cells of medium size which exhibit an irregular distribution of chromidial substance According to Bruce (1906), the visceral efferent neurons are not strictly limited to the intermediolateral cell column He recognized an apical group and a group situated in part in the central gray substance which he regarded as components of the visceral column He also emphasized the asymmetry and partial segmentation of the intermediolateral columns In Golgi preparations of embryos of the Chiroptera, Poljak (1924) traced axons from both the intermediolateral column and the intermediate zone into the ventral nerve roots On the basis of these findings he concluded that in this group of mammals visceral neurons occur not only in the intermediolateral cell column but also in the entire intermediate zone

Gagel (1928) described the neurons in the intermediolateral column in man as club- or pear shaped or oval and approximately one-half the size of the anterior horn cells Although, as observed in sections of the cord, many of these neurons appear uni- or bipolar, he regarded them all as multipolar In general they exhibit an irregular distribution of chromidial substance As compared with the neurons in the anterior gray column, the nucleus-plasma ratio favors the nucleus Gagel did not regard the forms of these neurons as significant since they are highly variable and, in a large measure seem to be determined by the arrangement of the fibers in relation to which neurons are located and other factors in the immediate environment He regarded the nucleus-plasma ratio and the size and distribution of the chromidial bodies as more significant than cell form

The neurons in the intermediate zone according to Gagel, commonly appear elongated or somewhat triangular, in sections of the cord and exhibit a relatively uniform distribution of finely granular chromidial substance They are of medium sizes and commonly occur in groups of two or three As compared with the neurons in the anterior gray column, the nucleus-plasma ratio favors the nucleus Although these neurons differ morphologically from those in the intermediolateral column Gagel regarded them as visceral in function

The intermediolateral cell column extends from the middle of the eighth cervical to the lower level of the first lumbar segment Gagel found a few cells which probably belong to this column in the second lumbar segment at the lateral border of the intermediate zone He observed neurons of the types described as intermediate zone cells in the region between the anterior and posterior gray columns throughout the entire length of the spinal cord

Spinal Autonomic Centers —Centers through which vasomotor activity, pilo-erection and perspiration are regulated are present throughout the thoracic and upper lumbar segments of the spinal cord These functions

in the head, neck and arms are regulated through centers in the *upper four* or five thoracic segments The upper two or three thoracic segments also include preganglionic neurons involved in the sympathetic innervation of the lacrimal glands Vasomotor activity, pilo-erection and perspiration in the upper trunk region are regulated through centers in the fourth to the ninth thoracic segments, below the umbilicus, through centers in the ninth or tenth thoracic to the second *lumbar segment, and in the lower extremities* through centers in the twelfth thoracic to the second lumbar segment inclusive

The pupillodilator, or so-called ciliospinal, center is located in the eighth cervical and first and second thoracic segments of the cord Cardiac

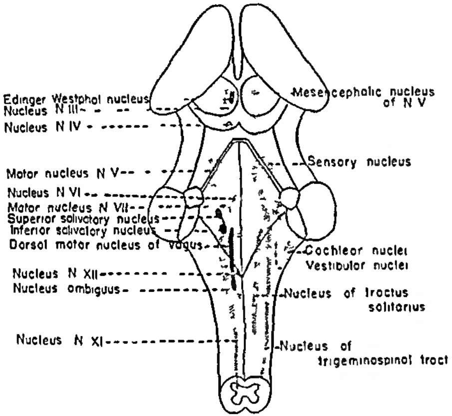

FIG 20 —Dorsal view of the human brain stem with the nuclei of the cranial nerves projected on the surface The motor nuclei are represented on the left side the sensory nuclei on the right side

accelerator centers are present in all the thoracic segments of the spinal cord from the second to the fifth or sixth inclusive Cannon, Lewis and Britton (1926) have shown that complete elimination of the cardiac accelerators in the cat requires interruption of the visceral rami or extirpation of the thoracic sympathetic trunk as low as the sixth or seventh thoracic segments Ionescu and Enachescu (1928) and Kuntz and Morehouse (1930) also traced cardiac rami from the sympathetic trunk as low as the sixth thoracic segment in man On the basis of these findings, it may be assumed that the corresponding segments of the spinal cord contain cardiac accelerator neurons The abdominal viscera receive impulses via the splanchnic nerves from centers in the fourth thoracic to the second lumbar segment of the spinal cord The sympathetic genito urinary and

recto-anal centers are located in the first and second lumbar segments, the parasympathetic centers in the second, third and fourth sacral segments

General Visceral Efferent Nuclei in the Brain Stem.—The general visceral efferent fibers of the cranial nerves arise from cells in a series of nuclei: the dorsal motor nucleus of the vagus, the salivatory nucleus and the Edinger-Westphal nucleus, which constitute the general visceral efferent column in the brain stem (Fig. 20). These cells are of small and medium sizes, with relatively large nuclei. The chromidial substance is only poorly developed and exhibits an irregular distribution (Malone, 1913).

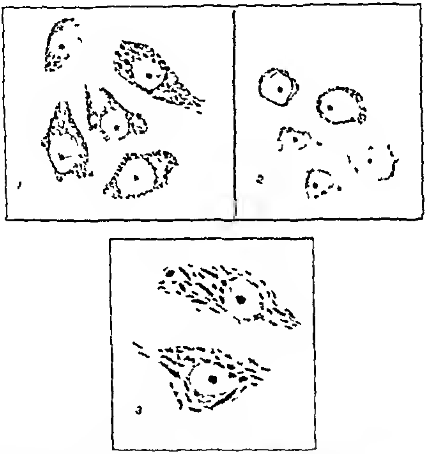

Fig. 21.—Efferent nerve cells from the medulla oblongata of the lemur: *1* and *2*, visceral efferent cells from the dorsal motor nucleus of the vagus; *3*, somatic efferent cells from the hypoglossal nucleus. (Malone.)

The dorsal motor nucleus of the vagus lies subjacent to the ala cinerea of the rhomboid fossa and dorsolateral to the hypoglossal nucleus. The efferent fibers arising in this nucleus are widely distributed to the parasympathetic ganglia in relation to the thoracic and abdominal viscera, for the innervation of the involuntary musculature of the heart, respiratory passages, esophagus, stomach, small intestine, biliary system, pancreas, etc. According to Malone (1913), the dorsal motor nucleus of the vagus in the lemur and monkey includes neurons of two distinct types (Fig. 21). The oral portion is composed of small neurons with relatively large nuclei and a meager supply of chromidial substance. The middle portion is composed of medium-sized neurons with a more abundant supply of chromidial sub-

stance The nucleus-plasma ratio of these cells, as compared with that of the small ones, favors the cytoplasm, as compared with that of the somatic motor neurons, it favors the nucleus The caudal portion is composed mainly of small neurons but contains some which are similar to the large ones in the middle portion According to Malone the axons of the small neurons supply smooth muscle and glands, those of the medium-sized ones supply heart muscle On the basis of these findings he designated the portion of the dorsal motor nucleus of the vagus which contains the medium-sized neurons the *nucleus cardiacus nervi vagi*

The nucleus salivatorius lies in the reticular formation at the junction of the pons and medulla oblongata As determined by stimulation experiments in the monkey (Magoun and Beaton, 1942), it lies between the genu of the facial nerve and the nucleus of the hypoglossal and extends from the medial plane lateralward and ventralward through the reticular formation

The efferent fibers arising from the more caudal portion or *nucleus salivatorius inferior*, are conveyed via the glossopharyngeal nerve to the otic ganglion Those arising from the rostral portion, or *nucleus salivatorius superior*, are conveyed via the chorda tympani to the submaxillary ganglion

The Edinger-Westphal nucleus is situated in the rostral portion of the nucleus of the oculomotor nerve It is composed of small neurons whose axons traverse the oculomotor nerve as preganglionic fibers to the ciliary ganglion, for the innervation of the intrinsic musculature of the eye

Other Autonomic Centers in the Medulla Oblongata and the Pons — A vasoconstrictor center in the medulla oblongata was recognized by Owsjannikoff as early as 1871 In a series of experiments in which the brain stem was transected at successive levels from above downward, he first observed a fall in blood pressure when the section was made at the middle level of the pons Sections made at lower levels resulted in still further lowering the blood pressure The results of more recent experimental studies have afforded a basis for the localization of the vasoconstrictor center in various mammals In the rabbit it is located in the floor of the upper part of the fourth ventricle approximately 2 5 mm from the medial plane in a position coinciding with that of the superior olive The results of experiments on other laboratory animals, reported by Nordmann and Muller (1932), indicate that this center is located in the substantia reticularis grisea in the upper part of the medulla oblongata

In a series of experiments involving electrical stimulation of the floor of the fourth ventricle in cats, Ranson and Billingsley (1916) observed a marked drop in blood pressure when the electrode was inserted under the clava just lateral to the obex On the basis of this finding they suggested that this area might include a true depressor center The results of certain later investigations do not fully corroborate this finding (Schilf, 1926), but it is known that depressor reflexes due to stimulation of the labyrinth (Spiegel and Demetriades 1924) or the depressor nerve (Spiegel and Yashin, 1928) persist after complete transverse section of the mesencephalon In experiments carried out on decerebrated animals, Yi (1938) observed that reflex lowering of the blood pressure elicited by stimulation of various afferent nerves was not abolished by cauterization of the vasoconstrictor center, but was abolished by destruction of an area adjacent to the obex

On the basis of this result, he concluded that there is an independent reflex center in the medulla oblongata through which vasoconstriction may be inhibited. Dowman *et al* (1939) also reported experimental data which indicate the existence of a depressor reflex center in the medulla oblongata.

That puncture of the floor of the fourth ventricle in a definitely circumscribed area results in hyperglycemia and glycosuria was known to Claude Bernard. Experimental data obtained by later investigators also indicate the existence of a center in the medulla oblongata which exerts a regulatory influence on sugar metabolism. In attempting to localize this so-called sugar center Brugsch, Dresel and Lewy (1923) observed that puncture of the rostral portion of the dorsal motor nucleus of the vagus resulted in hypoglycemia while puncture of the caudal portion of this nucleus resulted in hyperglycemia and glycosuria. According to Toenniessen (1924) it seems more probable that the puncture which resulted in hyperglycemia and glycosuria did not strike the vagus nucleus but an aggregate of cells outside this nucleus which is related to the autonomic system. In view of the existence in the diencephalon of a center which exerts a regulatory influence on carbohydrate metabolism, it has been suggested by some investigators that the above results of puncture of the floor of the fourth ventricle could be explained most satisfactorily on the assumption that descending fibers from the sugar center in the diencephalon and not a specific group of neurons in the medulla oblongata were stimulated. Brooks (1931), however, demonstrated reflex hyperglycemia following transection of the brain stem below the mesencephalon. On the basis of his experimental findings he concluded that there exists, in the floor of the fourth ventricle just below the middle of the brachium pontis and in close proximity to the vasomotor center, a neural mechanism through which reflex rises in blood sugar may be brought about by stimulation of an afferent nerve at least in anesthetized cats. In spite of the existence of this center, the diencephalic center probably must be regarded as the chief center for the nervous regulation of carbohydrate metabolism.

The existence of a center adjacent to the rostral half of the inferior olivary nucleus which plays a role in the regulation of respiration has long been known. New data bearing on the localization of this center in the cat and the monkey have been reported by Pitts (1940) and Beaton and Magoun (1941). According to their findings an inspiratory center is located dorsal to the rostral half of the inferior olivary nucleus. It includes the inferior reticular nucleus. In the monkey it extends from the medial plane 4 mm lateralward. At its caudal extremity it is somewhat narrower and lies adjacent to the hypoglossal nucleus. The area involved in the expiratory center is somewhat more extensive and surrounds the inspiratory center. With respect to their anatomical locations the respiratory centers in the monkey coincide in general with those in the cat.

The pons includes a center which is functionally related to the respiratory center in the medulla and connected with it through descending fibers (Lumsden 1923, Stella, 1939, Pitts *et al* 1939). Lumsden designated it the "pneumotaxic" center. It is located bilaterally in the ventral portion of the tegmentum close to the medial plane in the rostral few millimeters of the pons.

Autonomic Centers in the Diencephalon.—**Hypothalamus.**—*Nuclear Configuration.*—The diencephalic nuclei which are known to be function-

ally related to the autonomic nerves are located mainly in the hypothalamus and the walls of the third ventricle They are included in the paleothalamus, *i e*, the older portion of the diencephalon The hypothalamus occupies the ventral portion of the diencephalon It includes 15 to 20 nuclear aggregates of gray matter not all of which are clearly delimited, the optic chiasm, the supraoptic commissures and the hypophysis All the hypothalamic nuclei probably are functionally related, although not exclusively, to the autonomic system Certain adjacent nuclear aggregates in the preoptic area, which does not properly belong to the hypothalamus, also subserve autonomic functions

The histological structure of the hypothalamus has occupied the attention of not a few investigators Our present knowledge regarding the anatomical relationships of the hypothalamic nuclei and the cytological characters of their constituent neurons is based in a large measure on the early studies of Malone (1910–1914) Among the more recent investigators who have contributed to our knowledge of the topographic arrangement, the histologic delimitation and the anatomic connections of the hypothalamic nuclei may be mentioned Spiegel and Zweig (1915–1917) Greving (1923–1935), Gurdjian (1925–1928), Gagel (1928), Grunthal (1929–1933), Nicolesco and Nicolesco (1929), Rioch (1929), Huber and Crosby (1930), Morgan (1930), Loo (1931), Krieg (1932), Laruelle (1934), Roussy and Mosinger (1934, 1935), Crouch (1934), Papez and Aronson (1934), Clark (1936, 1938), Atlas and Ingram (1937), Kirgis (1940), and Ingram (1940)

For purposes of description, the hypothalamus in man may conveniently be subdivided into four regions the supraoptic middle region located above the optic chiasma and rostral to it, the tuberal or infundibular middle region located in relation to the infundibulum, the mammillary middle region which occupies the caudal portion of the hypothalamus including the mammillary bodies, and the lateral region

The supraoptic middle region includes the nuclei supraopticus, paraventricularis, suprachiasmaticus, supraopticus diffusus and the anterior hypothalamic area The nucleus supraopticus overlies the proximal portion of the optic tract and usually is incompletely separated by the latter into a relatively large anterolateral and a small posteromedial portion Its constituent neurons are mainly cells of relatively large sizes The nucleus paraventricularis, as observed in transverse sections of the hypothalamus, lies in intimate relation to the wall of the third ventricle and medial to the column of the fornix In sagittal sections (Fig 22) it appears triangular with the base of the triangle dorsalward Most of its constituent neurons are comparable to those of the nucleus supraopticus but they are less closely aggregated Between the larger neurons are some small ones comparable to the small neurons of the periventricular system The nucleus suprachiasmaticus is a small nucleus located against the dorsal surface of the optic chiasm and adjacent to the beginning of the supraoptic recess of the third ventricle Its constituent neurons are relatively small cells It probably is a constituent portion of the periventricular system The nucleus supraopticus diffusus consists of a poorly defined band of small neurons lying adjacent to the supraoptic commissures The anterior hypothalamic area is located between the supraoptic nucleus and the ventral end of the paraventricular nucleus It includes mainly small neurons

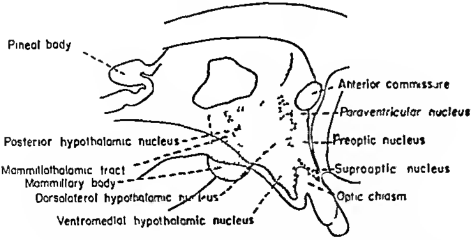

FIG 22 —Diagram of the hypothalamic nuclei in man as viewed from the ventricular surface (redrawn from Clark)

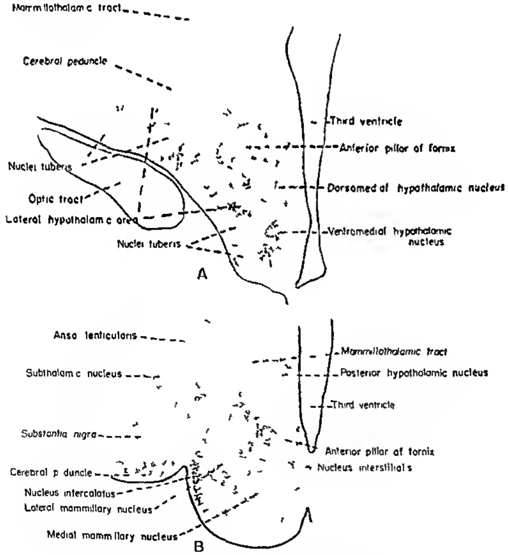

FIG 23 —Transverse sections of the human hypothalamus through (A) the tuber cinereum and (B) the mammillary bodies

The tuberal or infundibular middle region (Fig 23, *A*) includes the nuclei hypothalamicus ventromedialis, and hypothalamicus dorsomedialis and the dorsal and posterior hypothalamic areas The nucleus hypothalamicus ventromedialis is located adjacent to the ventricular surface of the tuber cinereum and immediately behind the nucleus supraopticus Its constituent neurons are relatively small and closely aggregated The nucleus hypothalamicus dorsomedialis lies adjacent to the dorsal border of the nucleus hypothalamicus ventromedialis and in essentially the same relation to the ventricular surface of the tuber cinereum It is continuous dorsally with the dorsal hypothalamic area and rostrally with the dorsal part of the anterior area Medially it can hardly be differentiated from the periventricular system Its constituent neurons are mainly small and not closely aggregated The dorsal hypothalamic area lies dorsal to the nucleus hypothalamicus dorsomedialis and extends from the dorsal part of the anterior hypothalamic area to the posterior area It comprises relatively few small neurons The posterior hypothalamic area occupies the border zone between the tuber cinereum and the mammillary body It is bounded laterally by the fornix and the mammillothalamic tract and is continuous dorsally with the midline nuclei of the thalamus It includes the nucleus hypothalamicus posterior which is characterized by closely aggregated small neurons among which larger ones are dispersed either singly or in small groups

The caudal or mammillary region comprises mainly the corpora mamillaria, a pair of rounded bodies, one on either side of the medial plane, situated in the interpeduncular fossa immediately in front of the posterior perforated area Each mammillary body includes three nuclei, the nuclei mamillaris medialis mamillaris lateralis and intercalatus (Fig 23, *B*) The nucleus mamillaris medialis comprises a relatively large, homogeneous aggregate of small neurons and is sharply delimited by a capsule of myelinated fibers Immediately in front of this nucleus and between it and the nucleus hypothalamicus ventromedialis is an aggregate of small neurons, the nucleus premamillaris The nucleus mamillaris lateralis is comparatively small in man Its constituent neurons are smaller than those of the nucleus mamillaris medialis and more closely aggregated The nucleus intercalatus is relatively large in man and occupies a lateral position in the mammillary body It is continuous at its rostral border with the lateral hypothalamic area Its constituent neurons are larger than those of the other mammillary nuclei

The lateral region comprises mainly the lateral hypothalamic area This area is situated lateral to the plane of the anterior pillar of the fornix and is continuous rostrally with the lateral preoptic area Its caudal portion is relatively narrow but extends to the tegmental portion of the midbrain The lateral area is traversed by the medial forebrain bundle and includes scattered groups of relatively large neurons In addition to these scattered neuron groups it includes two or three aggregates of small neurons in the lateral portion of the tuber cinereum, known as the nuclei tuberis (Fig 24, *B*)

Hypophysis — The hypophysis is a small rounded or ovoid glandular structure lodged in the hypophyseal fossa in the floor of the cranium It is attached to the hypothalamus by means of the infundibulum which arises from the floor of the third ventricle in the region of the tuber cinereum

The hypophysis comprises an anterior and a posterior lobe. The latter, which is the smaller of the two lobes, is continuous with the infundibulum. Like the latter structure, it is derived from the neural tube. The anterior lobe arises from the buccal ectoderm. Nerve fibers arising mainly in the supraoptic region and the tuber cinereum extend into the hypophysis where they terminate mainly in the posterior lobe. These fibers collectively constitute the hypothalamico-hypophyseal tract (Fig. 25).

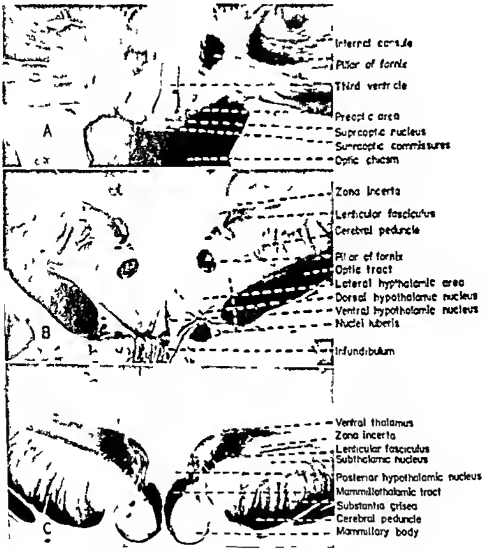

FIG. 24.—Transverse sections of the human hypothalamus through (A) the supraoptic region, (B) the infundibular region and (C) the mammillary region.

Neuron Classification.—On the basis of an intensive cytological study of the hypothalamic nuclei and their known fiber connections in the cat, Kirgis (1940) advanced the hypothesis that the neurons in these nuclei may be classified in four categories according to their anatomical and functional relationships. These have been designated peripheral visceral efferent, central somatic efferent, central visceral efferent and associational. The peripheral visceral efferent neurons are large spherical or polyhedral cells with coarse chromidial granules aggregated in the per-

ipheral zone and some chromidial substance in dust-like particles in the perinuclear zone The central somatic efferent neurons are comparable in sizes and forms to those of the previous category and exhibit coarse, discrete chromidial bodies which are fairly uniformly distributed throughout the cell body The central visceral efferent neurons are cells with spheroid or polyhedral cell bodies, mainly of medium sizes Their chromidial bodies are smaller than those in the neurons of either of the preceding categories These bodies frequently occur aggregated in the peripheral zone, but sometimes appear in clumps in certain portions of the cell body The associational neurons are relatively very small fusiform or spheroid cells with fine chromidial granules distributed mainly in the perinuclear zone

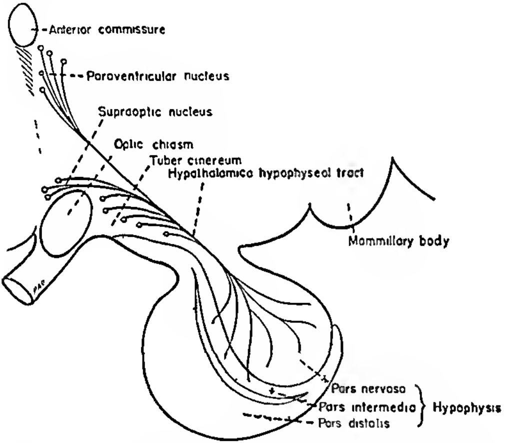

FIG 25 —Diagram illustrating the hypothalamico hypophyseal tract (redrawn from Clark)

The functional requirements of the hypothalamus obviously demand neurons of these four categories, but it must not be assumed that all hypothalamic neurons can be recognized as belonging to one or another category, since many which, on the basis of their anatomical relationships belong to one category are cytologically similar to some of the neurons of another category In the hypothalamus of the cat, according to Kirgis, most of the neurons are central visceral efferent Associational neurons apparently are next in abundance

In view of the known afferent fiber connections in the hypothalamus and the efferent conduction pathways which arise in it, to be described presently, most of the hypothalamic nuclei must include central visceral efferent and associational neurons Some of them must also include central

somatic efferent neurons The neurons whose axons enter the hypophysis via the hypothalamico-hypophyseal tract obviously must be classified as peripheral visceral efferent neurons, since their axons terminate directly in relation to the effector tissue

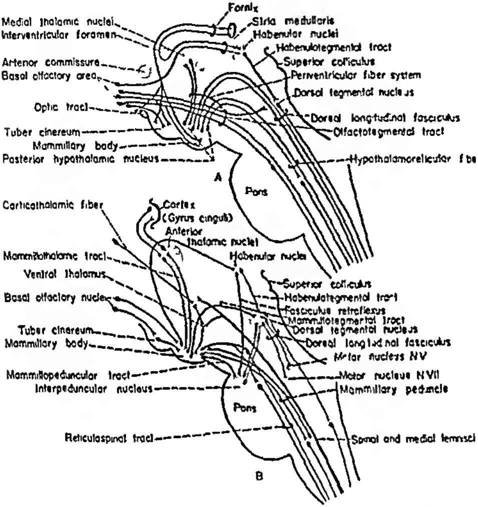

Fig 26 —Diagrams illustrating the chief connections of the hypothalamic nuclei and descending conduction pathways

Fiber Connections —The hypothalamic nuclei are intimately interconnected with one another and with adjacent thalamic nuclei through abundant internuclear fibers They are also connected with more remote parts of the nervous system through afferent and efferent conduction systems (Fig 26) Most of the internuclear connections are essentially diffuse and have not been completely analyzed The paraventriculo-supraoptic system is a fairly compact aggregate of fibers which seems to be efferent with respect to the paraventricular nucleus but convincing proof that its fibers terminate in the supraoptic nucleus is wanting Fibers arising in the paraventricular nucleus also enter the tuber cinereum but their sites of termination remain unknown Another recognizable aggregate of fibers extends into the supraoptic nucleus along the optic tract, but the origin and destination of its fibers have not been determined The longer fiber tracts connected with the hypothalamus may be described as afferent and

efferent conduction systems, but it must be recognized that in some of these systems the direction of conduction has not been fully established but only suggested on the basis of theoretical considerations

Afferent Systems —The medial forebrain bundle is composed of fine unmyelinated fibers running longitudinally through the lateral hypothalamic area It probably includes both ascending and descending fibers According to Gurdjian (1927), it comprises septo-lateral cortico- strio-tuberculo- parolfacto- and olfacto-hypothalamic tracts and an olfacto-mammillary tract The bundle is quite apparent in the human brain but cannot readily be resolved into its component parts Data advanced by Krieg (1932) and Ranson and Magoun (1939) support the assumption that some of its fibers extend from the hypothalamus into the tegmentum of the mesencephalon The septo-hypothalamic fibers probably arise from neurons which are synaptically related to neurons in the frontal lobe of the cerebral cortex

The Cortico-Hypothalamic and Thalamo-Hypothalamic Tracts —Conduction pathways from the neocortex to the hypothalamus probably include relay stations in the thalamus Direct pathways from any part of the neocortex to the hypothalamus have not been demonstrated Fibers of cortical origin have been traced into various parts of the dorsal thalamus by various investigators, including Clark (1933), Mettler (1935) and Levin (1936) Clark (1938) also advanced certain data in support of the assumption that fibers arising in the frontal cortex reach the zona incerta in the ventral thalamus Thalamo hypothalamic fibers are incorporated in the periventricular system and the mammillothalamic tract Other fibers of thalamic origin which enter the hypothalamic nuclei are not aggregated in well defined bundles Some of the fibers passing between the zona incerta and the hypothalamus probably are afferents which terminate in the hypothalamus The thalamo hypothalamic fibers provide not only for the conduction of impulses emanating from the cerebral cortex but also relay into the hypothalamus somatic and visceral sensory impulses which reach the thalamus from all parts of the body

The *Fornix* which arises in the hippocampus may be regarded as a direct conduction pathway from the paleocortex to the hypothalamus Its fibers terminate mainly in the mammillary nuclei and the tuber cinereum It probably includes some efferent fibers

The *Stria Terminalis* consists mainly of fibers which arise in the amygdaloid nucleus Many of these fibers terminate in the preoptic and adjacent hypothalamic areas as far caudalward as the premammillary nucleus According to Clark (1938), most of the hypothalamic nuclei receive afferent fibers through this bundle

Lenticulo hypothalamic connections probably are effected mainly through the ansa peduncularis and the ansa lenticularis (Laruelle, 1934, Nicolesco and Nicolesco, 1934) These fibers arise mainly in the globus pallidus and terminate in the ventromedial hypothalamic nucleus (Fig 24)

The mammillary peduncle (Fig 26) is not easily demonstrable in man but undoubtedly includes both afferent and efferent fibers The ascending fibers which reach the hypothalamus through this tract arise at various levels in the brain stem, particularly the mesencephalon It may be regarded as one of the important afferent pathways to the hypothalamus (Papez, 1937, 1938)

Vago supraoptic connections have not been demonstrated anatomically but the assumption that there is a conduction pathway from the vagal centers to the supraoptic nuclei is supported by experimental data (Bronk *et al*, 1936, Clark and Wang 1939, Sattler, 1939, Huang, 1938) This pathway seems to be directly related to the supraoptico-hypophyseal tract

Efferent Systems — The mammillothalamic tract is a well defined fasciculus which arises in the mammillary body, mainly in the medial mammillary nucleus and terminates in the anterior thalamic nuclei, particularly in the anteroventral nucleus (Figs 24, C and 26) It is an important link in one of the chief hypothalamo-cortical connections since some of the anterior thalamic neurons in relation to which its fibers terminate send their axons into the cortex of the gyrus cinguli The mammillothalamic tract probably reaches its highest development in man

Diffuse hypothalamo-thalamic connections undoubtedly exist but specific information regarding them is wanting The anatomical data regarding the scattered fibers which connect hypothalamic and thalamic nuclei afford little information regarding the direction of conduction in them

The mammillotegmental tract is closely related in its origin to the mammillothalamic tract (Fig 26) It probably terminates mainly in the nucleus profundus of the tegmentum Certain data support the assumption that it also effects connections with the central (Gurjian, 1927) and dorsal (Roussy and Mosinger, 1935) tegmental nuclei In man fibers of the mammillotegmental tract mingle with descending fibers from other parts of the hypothalamus as they extend downward in the capsule of the red nucleus

The periventricular system and the dorsal longitudinal fasciculus are intimately associated with one another The dorsal longitudinal fasciculus was originally described by Schutz (1891) as an aggregate of fibers in the central gray matter around the aqueductus cerebri which receives contributions from the hypothalamus, all parts of the dorsal thalamus, the subthalamic nucleus and the ansa lenticularis The hypothalamic components of the periventricular system which join the dorsal longitudinal fasciculus arise throughout the hypothalamus but most abundantly in the posterior area (Ingram, 1940) The sites of termination of these fibers are not definitely known They probably effect connections at various levels in the tectal and tegmental nuclei in the brain stem

Diffuse descending fibers probably arising in all parts of the hypothalamus extend downward in large numbers particularly in the lateral hypothalamic area Such fibers mingle with those of the medial forebrain bundle and form its downward continuation This system of fibers includes some components of the periventricular system Physiological data support the assumption that below the level of the hypothalamus these fibers lie widely scattered in the lateral portion of the tegmentum They constitute an important part of the efferent conduction system from the hypothalamus

Autonomic Centers in the Mesencephalon —The existence of a reflex center in the mesencephalon through which tonic responses of the musculature of the urinary bladder may be elicited has been demonstrated experimentally by Langworthy and Kolb (1938) Langworthy and Rosenberg (1939) also demonstrated the existence in the mesencephalon of reflex mechanisms through which the tonicity of the smooth muscle of the rectum is regulated Transection of the brain stem at the upper border of

the mesencephalon, in their experiments, resulted in hyperexcitability of the rectum to stretch stimuli Transection of the medulla oblongata, on the other hand, resulted in abolition of the response to stretch stimuli and partial loss of the normal tonus of the rectal musculature

Autonomic Representation in the Corpus Striatum—Experimental data which seem to indicate that impulses emanating from the corpus striatum exert an influence on visceral functions are not wanting For example, changes in the state of contraction of the smooth muscle of the pupil intestine, bladder, uterus and blood vessels have been observed following stimulation of the corpus striatum Due to the intimate relationship of the fibers of the internal capsule to the corpus striatum, however, it is quite impossible to stimulate the corpus striatum without at the same time exciting descending fibers of cortical origin In experiments reported by Spiegel and Takano (1928) stimulation of the corpus striatum, following degeneration of all corticifugal fibers on that side, neither resulted in contraction of the pupil nor of the blood vessels, whereas stimulation of the corpus striatum on the normal side elicited contraction of both the pupil and the blood vessels Stimulation of the corpus striatum following degeneration of the internal capsule also failed to elicit contraction of the musculature of the urinary bladder On the basis of these observations, they concluded that the contraction of smooth muscle elicited by stimulation of the corpus striatum is due mainly to excitation of fibers of cortical origin and not to stimulation of neurons in the corpus striatum

A direct influence of impulses emanating from the corpus striatum on the lower autonomic centers is not precluded Lesions of the corpus striatum undoubtedly result in increased body temperature, but the chief centers for the regulation of body temperature are located in the hypothalamus According to Spiegel and Reynolds (1930), puncture of the head of the caudate nucleus results not only in fever but also in polyuria and an increase in the specific gravity of the urine The NaCl content of the urine is appreciably increased (Tokay 1931) These results were observed only following lesions which involved the anterior horn of the lateral ventricle or the cortex and its underlying fibers close to the wall of the ventricle Simple injury of the cortical substance or the caudal part of the corpus striatum was ineffective On the basis of these experimental results, Spiegel (1932) expressed the opinion that the anterior portion of the corpus striatum exerts an influence particularly on the water-salt balance of the body through its fiber connections with the tuber cinereum

Autonomic Representation in the Cerebral Cortex—The functional activities of the visceral organs are regulated and controlled through centers in the brain stem and spinal cord but they are not free from influences emanating from the cerebral cortex Some of the data which indicate a cortical influence in the control of visceral functions are not new For example Eulenberg and Landois (1876) observed a fall in skin temperature of the contralateral extremities in response to stimulation of the cerebral cortex in the postcentral region in dogs and rabbits, and a rise in skin temperature of the contralateral extremities following extirpation of the same cortical areas Gowers (1888) reported vascular changes in the paralyzed extremities of hemiplegic patients Lewandowsky (1907) reported a rise in splanchnic blood pressure in response to stimulation of a certain area in the frontal cortex in the cat Bechterew (1911) advanced

certain experimental data which he interpreted as indicating an effect of stimulation of certain cortical areas on the cardiac rhythm and the blood pressure. He also observed increased skin temperature on the contralateral side in man in cases of cortical injury. Increased skin temperature of the affected extremities of patients with hemiplegia immediately following the onset of the paralysis and decreased skin temperature of the affected extremities in chronic cases has since been observed repeatedly. The excessive pilo-erector activity on the hemiparetic side which has been recorded in many cases affords a clearer indication of disturbed autonomic activity than the changes in skin temperature, since the vascular changes which take place in paralyzed extremities are due in part to atrophy and other changes in the tissues.

The concept of autonomic representation in the cerebral cortex now rests upon the firm foundation afforded by the results of numerous experimental studies, including those of Langworthy and Richter (1930), Fulton *et al.* (1934), Bucy (1934), Mettler (1935, 1936), Kennard (1937), Pinkston and Rioch (1938), Crouch and Thompson (1939), Baily and Sweet (1940) and Fulton (1939, 1940). All autonomic functions probably are influenced by impulses emanating from the cerebral cortex but no cortical areas have been recognized as essentially autonomic.

Fibers of cortical origin have been traced into the hypothalamus particularly from the precentral and parietal areas. Fibers of cortical origin through which visceral functions are influenced also terminate at levels in the brain stem below the diencephalon. The major cortical influence in the regulation of autonomic functions undoubtedly emanates from the precentral area, including the motor and premotor zones. The latter probably is more definitely related to the autonomic nerves than the former. The importance of these areas, particularly areas 4 and 6 of Brodmann, in the regulation of visceral functions is evidenced also by clinical observations (Christiansen, 1939). Autonomic reactions elicited by stimulation of sensory areas (Crouch and Thompson, 1939) and the orbital surface of the frontal lobe (Baily and Sweet, 1940) also have been reported. The autonomic reactions elicited by stimulation of a sensory cortical area, according to Crouch and Thompson, do not depend on actual neural connections with the motor area, but probably result from sensory impulses conducted to the hypothalamus.

Cortical influences on autonomic functions are carried out through both the sympathetic and the parasympathetic nerves, but no circumscribed cortical areas have been recognized which are functionally related to one of these systems and not to the other. Stimulation of a given cortical area, furthermore, may affect various autonomic functions equally. Consequently, it may be assumed that in general the autonomic system is affected as a whole by impulses emanating from one cortical area. Certain data support the assumption that the major cortical influence in the regulation of given visceral functions emanates from areas which are closely related to the cortical areas respectively which influence the corresponding somatic functions.

Autonomic Conduction Pathways in the Brain Stem and the Spinal Cord.—In the lower levels of the diencephalon the fibers which conduct impulses from the hypothalamic centers downward lie widely scattered. Most of them emerge from the lateral hypothalamic areas and traverse the central and tegmental portions of the mesencephalon and the tegmental

portion of the pons (Magoun, 1940) According to Beattie, Brow and Long (1930), experimental lesions in certain of the hypothalamic nuclei are followed by descending degeneration into the spinal cord indicating that the tracts in question pass partly into the reticular formation of the brain stem and partly into the intermediolateral cell column in the spinal cord These descending fibers are partly crossed but mainly uncrossed They become concentrated in the ventral portion of the posterior longitudinal bundle and the dorsal portion of the reticular formation of the medulla oblongata According to Allen (1932), the reticulospinal tracts are in part visceral Since many of the short fibers which descend from the hypothalamus terminate in the reticular formation in relation to neurons whose axons descend in the reticulospinal tracts, the latter play a role in the conduction of visceral impulses from the hypothalamus as well as from the reticular formation of the mesencephalon and pons

The pathways through which autonomic impulses are conducted downward in the brain stem and spinal cord have been investigated particularly by Ranson and his collaborators Their findings, as summarized by Magoun (1940), support the conclusion that these pathways include some long fibers and an extensive system of short fibers arranged in relays In the medulla oblongata the descending autonomic pathways lie mainly in the lateral portion of the reticular formation In the spinal cord they lie mainly in the anterior portion of the lateral funiculus Most of these fibers are limited to one side, but some cross the medial plane in the brain stem or at lower levels in the spinal cord The descending pathways which conduct vasomotor impulses from the hypothalamus, as indicated by data advanced by Harrison Wang and Berry (1939), include crossed and uncrossed components Some vasomotor impulses which cross in the brain stem probably cross again in the spinal cord Pathways through which impulses of hypothalamic origin reach the urinary bladder, according to Wang and Clark (1940), include decussations in the brain stem and in the lower lumbar segments of the spinal cord but none in the intervening portions of their courses The pathways which conduct impulses downward from the respiratory centers in the medulla oblongata, according to Pitts (1940), traverse the anterior funiculus and the anterior portion of the lateral funiculus in the spinal cord The descending pathways which subserve heat elimination functions in the cat, according to Beaton, Leininger and McKinley (1943), appear to be concentrated in the intermediate and lateral portions of the dorsal tegmentum in the mesencephalon and the pons, those subserving heat conservation appear to be located mainly in the lateral tegmental region In certain cases the heat elimination functions were abolished by appropriately placed lesions while heat conservation activities were maintained, thus indicating a dual temperature regulating system These results also support the assumption that tegmental pathways are of greater importance than the periventricular system in efferent conduction from the hypothalamus In the monkey, according to Beaton and Leininger (1943), the conduction pathways for sweating are located in the lateral and anterior funiculi in the spinal cord and are completely or almost completely crossed The crossing takes place close to the level at which the fibers in question terminate in the intermediolateral cell column The pathways for pilo-erection and shivering appear to be located in the anterior funiculus Some of their component fibers cross the medial plane but most of them terminate on the same side

CHAPTER IV

GENERAL PHYSIOLOGY

Functional Connections of the Autonomic with the Central Nervous System.—The neurons in the autonomic ganglia and plexuses are functionally related to the central nervous system through the general visceral efferent, or preganglionic components of the cerebrospinal nerves. The normal physiological activity of the autonomic nerves, with certain exceptions, requires the integrity of the preganglionic neurons. Certain experimental data strongly suggest that, in connection with peripheral tissues the sympathetic ganglion cells are capable of some independent activity (Tower and Richter, 1932). The enteric plexuses are dependent upon their functional connections with the central nervous system to only a limited extent. For an account of their independent functional activity see Chapter X.

According to the current teaching the preganglionic neurons cannot function in the absence of autonomic ganglia. Langendorff (1901) reported two experiments on cats in which preganglionic stimulation was again effective three and a half months after extirpation of the superior cervical sympathetic ganglion. Langley and Anderson (1904) obtained an apparently similar result in 2 cases out of 8 but later microscopic examination, in both these cases, showed that some of the nerve cells in the superior cervical ganglion had not been removed; consequently, some of the regenerating preganglionic fibers reestablished functional connections with the remaining ganglion cells. Other experiments of the same kind, some of which involved extirpation of the ciliary, and others extirpation of the stellate ganglion carried out by Langley, yielded only negative results. On the basis of experimental studies of this kind, it has been assumed that the axons of preganglionic neurons are incapable of effecting functional connections with tissues in which efferent connections are normally effected only by postganglionic fibers.

The results of experimental studies reported by Ballance (1931) and Beattie, Duel and Ballance (1932) seem to support the hypothesis that preganglionic neurons have the capacity to effect direct functional connections with striated muscles. In their experiments, carried out on cats and baboons, the proximal portion of the divided sympathetic trunk was connected with the distal portion of the divided hypoglossal, descendens hypoglossi, facial or phrenic nerve. The larger fibers in the cervical sympathetic trunk, as was later determined histologically, grew distalward in the nerve trunk with which the anastomosis had been effected whereas the smaller fibers grew in but a short distance. After functional connections with the muscles had been established, faradic stimulation of the cervical sympathetic trunk proximal to the anastomosis elicited contraction of the muscles. In some of the animals apparently normal movements of the muscles in question were observed as early as three months after the anastomosis had been effected. Recovery of muscular activity was noted in all the animals allowed to survive for periods varying from 15 to 323 days. Stimulation of the hypothalamus such as results in dilatation

of the pupil in intact animals, resulted in muscular responses of the same type, in these experiments, in animals surviving 178 days or longer, as stimulation of the cervical sympathetic trunk proximal to the anastomosis

The capacity of preganglionic fibers to reestablish synaptic connections in the autonomic ganglia is amply demonstrated Even extensive injuries to preganglionic nerves undergo rapid restoration If their course is not blocked by scar tissue the axons of preganglionic neurons grow along their former pathway into the ganglion and reestablish functional connections with the ganglion cells in a relatively short time Kirgis and Ohler (1944) reported functional restoration of the sympathetic innervation of the iris and the nictitating membrane in the cat four months after section of the preganglionic fibers and removal of the stellate and upper thoracic sympathetic trunk ganglia The results of certain experimental studies involving artificial anastomosis of the distal portion of the cervical sympathetic trunk and the proximal portion of the vagus, phrenic or a convenient somatic nerve, also indicate that the interrupted fibers of these nerves may grow into the superior cervical ganglion and effect synaptic connections with the ganglion cells In experiments reported by Duel and Ballance (1932), in which the distal portion of the cervical sympathetic trunk was connected with the proximal portion of another nerve in the vicinity, *e g*, the hypoglossal superior laryngeal inferior laryngeal phrenic or fifth cervical, the ocular effects of cervical sympathectomy all disappeared, indicating that the fibers of the divided nerve had grown into the superior cervical sympathetic ganglion and established functional synaptic connections with the ganglion cells Marked improvement was noted sixty days after the operation and the eyes were restored to nearly normal after 100 to 120 days The first apparent change toward recovery was advancement of the eyeball Later, the pupil gradually dilated until it became equal to the one on the unoperated side The last sign to disappear was the prominence of the nictitating membrane the recession of which, in some of the experiments, was incomplete The results of experimental studies involving interruption of postganglionic fibers do not indicate that these fibers possess the capacity for regeneration (Tower and Richter, 1932, Kirgis and Ohler, 1944)

Functional Significance of Ganglion Cells—Individual preganglionic neurons effect synaptic connections with more than one ganglion cell Individual ganglion cells likewise are synaptically related to more than one preganglionic neuron Ganglion cells, consequently, receive impulses which probably differ qualitatively but they are essentially relay stations in visceral efferent conduction pathways The results of experiments carried out to determine whether they exert a modifying influence on efferent impulses which are relayed by them are not unequivocal

The pupillary reactions elicited by stimulation of the cervical sympathetic trunk have been compared with those elicited by stimulation of the plexus on the internal carotid artery by not a few investigators The effects on the iris of section of its preganglionic and postganglionic sympathetic nerves respectively also have been compared The results of these studies are not sufficiently in accord to warrant a conclusion regarding the effect of the sympathetic ganglion cells in question

Hofmann (1904) pointed out that stimulation of a single communicating ramus commonly results in activation of the entire end organ in

question For example the dilator pupillæ responds as a whole to stimulation of the white communicating ramus of any one of the thoracic nerves through which it is supplied but stimulation of postganglionic fibers contained in a single one of the long ciliary nerves results in contraction of only a limited portion of the dilator pupillæ muscle In the reverse experiment in which certain of the long ciliary nerves were cut previously, he also observed that stimulation of the cervical sympathetic resulted in contraction of only those parts of the dilator pupillæ which are innervated by the long ciliary nerves which remained intact Langley (1901) pointed out that dilatation of the entire pupil is sometimes brought about by stimulation of a single long ciliary nerve He assumed the existence of a preterminal plexus of postganglionic fibers through which impulses conducted by relatively few fibers might affect the entire dilator pupillæ muscle In view of our present knowledge of sympathin and its role in the mediation of sympathetic impulses this assumption is no longer necessary (page 105)

Certain investigators acting on the assumption that the effect of the ganglion cells might be more readily demonstrated in the nerves supplying the blood vessels than other autonomic nerves by virtue of the important role of the blood vessels in the nutrition of all the tissues have carried out similar experiments involving these nerves In some instances, the effects on certain blood vessels of stimulation of the pre- and postganglionic fibers respectively were compared In others the effects of removal of the ganglion cells were studied The results of such experiments do not indicate that the efferent impulse suffers any important modification by passing through the ganglion cells Schultz (1900) observed that effective stimulation of postganglionic fibers requires a stimulus of greater intensity than effective stimulation of the corresponding preganglionic fibers On the basis of this observation he advanced the opinion that impulses traversing the preganglionic fibers which are not of sufficient intensity to activate the ganglion cells may by summation reach the threshold of stimulation of these cells In the case of the superior cervical sympathetic ganglion Veach (1926) demonstrated that the pre- and postganglionic fibers are not equally sensitive to induction shocks but he obtained no evidence which seemed to indicate that impulses are modified quantitatively by passing through the ganglion The difference in the sensitivity of the pre- and postganglionic fibers to induction shocks probably is correlated with the difference in the caliber of the fibers

The character of the response elicited by stimulation of a postganglionic nerve as demonstrated by Bronk *et al* (1938), is not modified by separation of the nerve from the ganglion, consequently, there is no evidence of backfiring from the ganglion cells or of reflex connections within the ganglion According to their findings, a volley of impulses conducted by preganglionic fibers initiates a single temporally dispersed volley of postganglionic impulses The individual ganglion cells discharge each a single impulse in response to a preganglionic volley The temporal dispersion exhibited by the postganglionic volley is due to the differences in the conduction rates of the postganglionic fibers

At frequencies of not over 10 to 20 per second, either maximal or submaximal stimulation of a preganglionic nerve results in discharges of constant magnitude in the postganglionic fibers, showing activation of a

constant number of ganglion cells If the circulation through the ganglion is stopped, the numbers of ganglion cells which respond to single preganglionic volleys decrease progressively Perfusion of a ganglion with acetylcholine results in a marked increase in the number of ganglion cells which respond to a submaximal preganglionic volley It also induces either a random discharge of ganglion cells or a rhythmic discharge of single ganglion cells or closely synchronized ones Further data advanced by Bronk (1939) support the assumption that the frequency of impulses emanating from the central nervous system is modified by the autonomic ganglion cells

Afferent Neurons Functionally Associated with the Autonomic Nervous System —The afferent neurons which conduct visceral impulses into the central nervous system as well as all the peripheral afferent neurons which effect reflex connections in central autonomic centers are components of the cerebrospinal nerves, consequently, they are not included in the autonomic nervous system The afferent limb of an autonomic reflex arc may be either a visceral or a somatic afferent cerebrospinal nerve component

Afferent impulses arising in any part of the body may elicit reflex reactions carried out through autonomic nerves The question regarding the existence of autonomic neurons which are essentially afferent in character has been much discussed There are no data available at present which may be regarded as proving the existence of autonomic neurons which are incorporated in pathways through which afferent impulses are conducted into the central nervous system In general the autonomic neurons are efferent in function There is no clear evidence that either the ganglia of the sympathetic trunks or the cranial autonomic ganglia either include afferent neurons or constitute reflex centers in the ordinary sense On the contrary, both anatomic and physiologic data are available which demonstrate quite clearly that certain of the peripheral plexuses, *e g*, the myenteric and submucous plexuses, include reflex mechanisms and are capable of carrying out coordinated reflex activities independently of the central nervous system (see Chapter X) Reflex reactions mediated through the celiac and inferior mesenteric ganglia also have been demonstrated (see Chapter II)

Axon Reflexes —Although the data available at present speak against the existence of reflex connections in the autonomic ganglia (except the enteric and prevertebral) physiologic data are not wanting which strongly suggest that, under certain conditions, reflex reactions may be carried out through these ganglia Such data were recorded by Claude Bernard as early as 1864 Sokownin (1874) observed that after all the nervous connections of the inferior mesenteric ganglia except the hypogastric nerves were cut, stimulation of the central end of one hypogastric nerve elicited contraction of the bladder, the efferent impulses passing down the hypogastric nerve on the opposite side Langley and Anderson (1894) confirmed this finding

In experiments carried out on animals in which the spinal cord was completely destroyed or the preganglionic fibers connecting the portion of the sympathetic trunk in question with the spinal cord were severed so that no reflexes could be carried out through spinal centers, Langley (1900) found that when the sympathetic trunk was divided and its central

end was stimulated, contraction of the erector pili muscles and constriction of the cutaneous blood vessels took place in an area corresponding to the distribution of from one to four gray rami above the level at which the stimulus was applied. These responses were abolished by intravenous injection of nicotine or its application to the sympathetic ganglia in question and could not be elicited after the preganglionic fibers in the sympathetic trunk had undergone degeneration. It appeared to be evident, therefore, that the reactions in question were mediated through preganglionic fibers and neurons in the ganglia of the sympathetic trunk. On the basis of these findings Langley concluded that each preganglionic fiber which enters the sympathetic trunk gives rise to a number of branches through which it effects synaptic connections with several, perhaps many, ganglionic neurons. The preganglionic fibers which supply a compound ganglion, e. g., the superior and inferior cervical, may send all their branches to one ganglion. Those which enter a single segmental ganglion commonly traverse more than one ganglion and may give off collaterals which terminate in all these ganglia. In the lower thoracic, lumbar and sacral portions of the sympathetic trunk in the cat, according to Langley, the majority of the preganglionic fibers terminate through collaterals in three or more ganglia. When such preganglionic fibers are stimulated distally, under experimental conditions, the impulse travels centralward in the fiber and peripheralward in its collateral branches and may activate all the ganglionic neurons in relation to which these branches terminate. Langley explained all reflex phenomena elicited by stimulation of the preganglionic fibers following destruction of their connections with the central nervous system on this basis. Since they could not be regarded as reflexes in the ordinary sense, he called them pseudo-reflexes. Inasmuch as they depend on afferent conduction through preganglionic fibers, he also called them preganglionic axon reflexes.

Postganglionic axon reflexes, i. e., reflexes which are carried out through a single axon and its branches, also have been described. It has been assumed that stimulation of the peripheral portion of an axon or an axon collateral may give rise to impulses which travel centralward through the division of the fiber stimulated and peripheralward through its other divisions, thus calling forth a localized response in the end organ in question. Such reactions were described by Kuhne (1886) in skeletal muscles and more recently by various investigators in both somatic and visceral organs.

Speranskaja-Stepanowa (1925) reported certain phenomena which he regarded as postganglionic sympathetic vasodilator and vasoconstrictor axon reflexes in the frog. Wernoe (1925) also described viscero-cutaneous reflexes in fishes which he regarded as reflexes mediated through a single sympathetic neuron, the axon of which sends one branch to a visceral organ and another to the skin. Certain cutaneous manifestations in man also have been interpreted as due, at least in part, to localized axon reflexes (Breslauer, 1919).

Preganglionic axon reflexes have been observed mainly under experimental conditions. Reactions which have been interpreted as postganglionic axon reflexes have been observed under both experimental and apparently normal physiological conditions. To what extent either preganglionic or postganglionic axon reflexes play a role in the normal functional activity of the autonomic nerves as yet is unknown.

Antagonistic and Synergic Actions of Sympathetic and Parasympathetic Nerves.—The autonomic nervous system, as described in Chapter I, is made up of the sympathetic and parasympathetic divisions. The preganglionic neurons of the former division are components of the thoracic and upper lumbar nerves, those of the latter are components of certain of the cranial and sacral nerves. The internal organs are innervated through both sympathetic and parasympathetic nerves, consequently, they receive efferent impulses from widely separated centers in the central nervous system, the effects of which in general are antagonistic. For example, impulses reaching the heart through the parasympathetic nerves tend to inhibit, and impulses reaching it through the sympathetic cardiac nerves tend to accelerate cardiac rhythm. On the contrary, vagus impulses usually exert an excitatory influence on the gastro-intestinal musculature, and impulses conducted through the sympathetic nerves usually inhibit gastro-intestinal motility. The influence of the pelvic nerves on the large intestine is the same as that of the vagi on the more proximal parts of the alimentary canal. With regard to the genital organs impulses conducted through the hypogastric nerves exert a vasoconstrictor effect and impulses conducted through the pelvic nerves a vasodilator effect. Similar conditions also obtain in the cephalic region. Constriction of the pupil is brought about by impulses emanating from the midbrain through the preganglionic components of the oculomotor nerve and neurons in the ciliary ganglion. Dilatation of the pupil is mediated through preganglionic fibers arising in the upper thoracic segments of the spinal cord and neurons in the superior cervical sympathetic ganglion. The salivary glands likewise, are supplied by parasympathetic fibers from the otic and submaxillary ganglia and sympathetic fibers from the superior cervical sympathetic ganglion.

All blood vessels probably are innervated through sympathetic nerves. Those in certain parts of the body probably also are innervated through parasympathetic nerves. With certain exceptions vasoconstriction is mediated through sympathetic nerves. The sympathetic nerves to the peripheral blood vessels also include vasodilator fibers. There are no known pathways by which fibers belonging either to the cranial or sacral autonomic outflows reach the vessels of the extremities or the somatic portions of the trunk. It has been assumed by certain investigators that groups of parasympathetic cells are present in the spinal cord throughout the cervical and thoracic regions and that these cells send their axons out through the dorsal roots of the spinal nerves to be distributed to the peripheral blood vessels but anatomical proof of the existence in the dorsal spinal nerve roots of efferent fibers distributed to the peripheral blood vessels is not forthcoming.

The so-called antagonistic action of the sympathetic and parasympathetic nerves may be compared with the reciprocal action of the cerebrospinal nerves which supply the flexor and extensor muscles respectively which act on a given joint. When either the flexors or extensors contract in response to nerve impulses the opposing group undergoes a degree of relaxation but is not wholly devoid of tonus since impulses are received through its efferent innervation. In like manner, the sympathetic and parasympathetic nerves supplying a given organ maintain a functional balance. For example, an increase in cervical sympathetic tonus, resulting in dilatation of the pupil, is accompanied by a simultaneous diminution

of tonus in the parasympathetic nerves which innervate the sphincter pupillæ muscle. Dilatation of the pupil in response to cervical sympathetic stimulation probably is brought about, not only by contraction of the dilator pupillæ muscle, but in part also by relaxation of the sphincter pupillæ, due to diminished parasympathetic tonus. Splanchnic stimulation, likewise, brings about relaxation of the gastric musculature, a result which could not be obtained without simultaneous diminution of the tonic influence of the vagi. In general it may be assumed that increased sympathetic tonus is accompanied by a corresponding diminution of parasympathetic tonus and *vice versa*.

Although the sympathetic and parasympathetic nerves supplying a given organ usually produce opposite effects, stimulation of either a sympathetic or a parasympathetic nerve sometimes elicits not the usual but the opposite effect. This probably is determined by the initial tonic condition of the tissue involved or the hormonal content of the blood at the moment. On the other hand, certain autonomic nerves include both excitatory and inhibitory fibers. For example, the parasympathetic fibers supplying the bronchial and gastro-intestinal musculature exert an excitatory, and those supplying the heart an inhibitory influence, whereas the sympathetic fibers supplying the bronchial and gastro-intestinal musculature exert an inhibitory, and those supplying the heart an excitatory influence.

Regulation of Autonomic Functions Through Diencephalic Centers.—The diencephalic autonomic centers, located mainly in the hypothalamus, exert a significant regulatory influence in all autonomic functions and may be regarded as functionally superimposed on the lower autonomic mechanisms. These centers undoubtedly are capable of integrating complex autonomic reactions independently of influences from higher levels but they are functionally related to the cerebral cortex, from which they receive regulatory impulses.

Temperature Regulation.—The control of body temperature in warm-blooded animals, including man, involves regulation of heat production and regulation of heat elimination. Hypothalamic centers undoubtedly play major roles in both these functions, although other central mechanisms also are involved. Experimental data advanced by Aronsohn and Sachs (1885), Barbour (1912) and Spiegel and Reynolds (1930) support the assumption that mechanisms in the corpus striatum play a significant role in the regulation of body temperature. Extirpation of the cerebral hemispheres, including the corpora striata, in experimental animals, however, is not incompatible with the maintenance of normal body temperature but the capacity to maintain normal body temperature is lost following destruction of the hypothalamus (Isenschmidt and Schnitzler, 1914). This capacity also is greatly impaired by transection of the spinal cord in the cervical region, due to interruption of the descending conduction pathways from the hypothalamus to the preganglionic autonomic nuclei.

The end organs through which the nervous regulation of body temperature is brought about are mainly the blood vessels, sweat glands, and the internal organs whose metabolic processes tend to increase or inhibit heat production. The glands of internal secretion also play an important role in the regulation of body temperature. Although not entirely free from nervous influences, these glands, through their secretory activity,

may exert a direct influence on the metabolic processes through which heat is generated On the other hand the temperature-regulating centers may be activated directly by endocrine products in the blood stream In view of the many factors which influence the production and elimination of heat it is obvious that the organs involved in heat production and heat elimination must receive excitatory and inhibitory impulses from the temperature-regulating centers more or less constantly On the other hand, these centers must be influenced by every variation in temperature, both at the periphery and in the internal organs in part through nerve conduction, but mainly through the direct effect of the circulating blood on the temperature-regulating centers

The reactions of the temperature-regulating centers to the temperature of the blood flowing through them probably are of greater importance in the regulation of the body temperature than the reflex responses to thermal stimulation of the peripheral receptors In experiments carried out by Kahn (1904), raising the temperature of the blood in the carotid artery resulted in peripheral vasodilatation perspiration and heat dyspnea, all of which are common symptoms of overheating On the contrary, cooling of the blood supplying the hypothalamus resulted in increased metabolism in the internal organs and a consequent rise in body temperature Barbour (1912, 1913) and Hashimoto (1915) also found that changes in the body temperature can be brought about by changing the temperature of the heat-regulating centers by introducing water through fine cannulae inserted into the brain When cold water was introduced, the body temperature was raised, when warm water was introduced, the body temperature was lowered

In view of the physiological relationships of the temperature-regulating centers, we should expect that any pathological condition, which affects these centers directly, initiates strong afferent impulses which reach the thalamus or gives rise to toxic substances which circulate in the blood, might give rise to pathological changes in body temperature Most of the stimuli which give rise to fever probably exert a direct effect on the temperature-regulating centers Fever may also be produced by a variety of mechanical, chemical and physicochemical stimuli This knowledge affords a basis for the explanation of the constant occurrence of fever in certain cases of brain injury or other pathological lesions of the brain substance in proximity to the temperature-regulating centers in which infection is not a factor Such conditions as internal hydrocephalus and hemorrhage in the third ventricle, likewise, may give rise to fever due to mechanical pressure exerted on the hypothalamus High fever accompanying apoplexy, in many cases, is due at least in part to the effect of pressure on the temperature-regulating centers brought about by the hemorrhage which caused the disorder Pathological conditions which result in great pressure on the hypothalamus *e g*, certain cases of hydrocephalus also may cause a fall in body temperature due to paralysis of the temperature-regulating mechanisms

In summarizing the results of extensive experimental investigations of hypothalamic functions, carried out by his collaborators and himself, Ranson (1940) concluded that the hypothalamic mechanisms involved in the regulation of body temperature are arranged anteroposteriorly

Data advanced by Barbour (1939) and Erickson (1939) also support this conclusion

The hypothalamic neural mechanisms concerned in the protection of the body against hyperthermia are localized in the region in front of the optic chiasm and below the anterior commissure. Local heating of this region in experimental animals results in panting and secretory activity of the sweat glands. Superheated blood circulating through this region probably initiates the same reactions. Localized lesions in this portion of the hypothalamus result in impairment of the ability of the body to protect itself against overheating. In cats with localized lesions in this area panting does not occur even though the body temperature reaches 106° F. This is not due to damage to the motor mechanisms through which coordinated panting movements are brought about, since the latter are located farther caudally, probably in the mesencephalon (Clark, Magoun and Ranson, 1939). These centers receive hypothalamic impulses through fibers which descend in the lateral hypothalamic area. Cats in which these centers are freed from the regulatory influences emanating from higher levels by transection of the brain stem in the caudal portion of the diencephalon may exhibit decerebrate panting even though the body temperature is subnormal.

The hypothalamic mechanisms concerned in the protection of the body against hypothermia seem to be coextensive with the hypothalamic nuclei which are functionally related to the sympathetic nerves. Protection of the body against chilling is not seriously impaired by lesions of moderate size unless they are located bilaterally in the lateral hypothalamic area and near the caudal border. Large lesions in other parts of the hypothalamus, particularly in the caudal portion, result in impairment of this function to some extent. The neurons involved probably are at least in part identical with those which subserve vasoconstriction, pilo-erection and certain other sympathetic functions.

Certain clinical data support the assumption that the hypothalamus plays a role in the regulation of body temperature in man comparable to that which has been demonstrated experimentally, particularly in cats and monkeys. Davison and Selby (1935) reported a case in which the body temperature remained at approximately 92.4° for several weeks before death. Postmortem examination in this case revealed extensive destruction of the hypothalamus, including the lateral hypothalamic areas at the level of the mammillary bodies, caused by an angioma. Alpers (1936) reported two cases in which operations for tumors affecting the rostral portion of the hypothalamus were followed by rapidly developing hyperthermia and death. Postmortem examination in these cases revealed extensive damage to the gray matter in the walls of the third ventricle just behind the optic chiasm. Davison (1940) reported a series of cases in which impairment of the temperature regulating mechanisms was associated with lesions of the hypothalamus. In four of five patients with hyperthermia the lesions were localized in the rostral portion of the hypothalamus and extended into the lateral area on both sides. In four patients with hypothermia, the lesions extended into the caudal portion of the hypothalamus including the mammillary bodies and involved the lateral area bilaterally.

Carbohydrate Metabolism—The assumption that carbohydrate metabolism is influenced by impulses emanating from the hypothalamus seems to be supported by experimental data advanced by various investigators Hyperglycemia associated with lesions of the hypothalamus or following hypothalamic stimulation has been reported particularly by Aschner (1912), Camus and Roussy (1920), Camus, Gournay and Le Grand (1925), Sachs and MacDonald (1925), Beattie, Brow and Long (1930), Lewy and Grassmann (1935), Cleveland and Davis (1936), Ingram and Barris (1936) and others These data show clearly that carbohydrate metabolism may be influenced by hypothalamic stimulation or lesions in this region of the brain stem but do not prove that hypothalamic mechanisms play a predominant role in this phase of the general metabolism In evaluating the available data bearing on this problem Long (1940) has pointed out that although the hypothalamus may play some part in this function, the weight of evidence supports the assumption that the major part of the regulation of carbohydrate metabolism is effected through the activity of endocrine glands

Water Metabolism—The assumption that the hypothalamus plays a significant rôle in water metabolism has been advanced on the basis of both experimental and clinical data The production of polyuria by stimulation of the hypothalamus was reported by Eckhart as early as 1876 Polyuria and polydipsia are not uncommon phenomena associated with hypothalamic lesions particularly in the rostral area Some of the most significant studies bearing on the general problem of water metabolism have been carried out in an effort to determine the etiology and pathology of diabetes insipidus This disease is now known to be associated with a deficiency in the production of the antidiuretic hormone by the pars nervosa of the hypophysis, but it is causally related to the hypothalamus in so far as the changes in the hypophysis resulting in the arrest or retardation of the production of the antidiuretic principle are related to hypothalamic lesions Extirpation of the pars nervosa of the hypophysis or its atrophy due to interruption of the supraoptico-hypophyseal tract commonly result in retardation or complete arrest of the production of the diuretic hormone and consequent diabetes insipidus (Fisher, Ingram and Ranson, 1938)

The earliest extensive studies on the relation of the hypothalamus to diabetes insipidus are those of Camus and Roussy and their collaborators (1913–1925) The results of these studies seemed to warrant the conclusions that hypophysectomy without injury to the hypothalamus does not result in diabetes insipidus but this disorder may be produced in hypophysectomized animals by puncture of the hypothalamus It may also result from a lesion in the hypothalamus in the region between the optic chiasm and the cerebral peduncles without injury to the hypophysis

Since the assumption that a deficiency of the antidiuretic hormone produced by the pars nervosa of the hypophysis, or its complete absence, results in polyuria is supported by ample experimental data it seems highly probable that some pars nervosa tissue must have remained in the hypophysectomized animals which failed to develop diabetes insipidus There is no good reason to assume that diabetes insipidus can develop in complete absence of the hypophysis, since the diuretic influence of the pars distalis also has been removed

The results of more recent studies, particularly those of Ranson and his collaborators, have provided the basis for a more complete evaluation of the neurogenic factors in the causation of polyuria and polydipsia as observed in diabetes insipidus and in the regulation of water metabolism. The regulation of water exchange is mediated through hormonal agents but the production of the antidiuretic hormone is regulated through the supraoptico-hypophyseal tract. Interruption of this tract results not only in arrest of the production of the antidiuretic hormone in the pars nervosa of the hypophysis but also in atrophic changes in this part of the gland (Fisher, Ingram and Ranson, 1938). The hypothalamus, consequently, exerts a significant influence on water metabolism through the supraoptic nuclei and the supraoptico-hypophyseal tract. This point of view also is supported by the work of Ingram, Ladd and Benbow (1939) in which they consistently failed to recover antidiuretic substance from the urine of cats in which the nerve fibers extending from the hypothalamus to the pars nervosa of the hypophysis had been interrupted.

The displacement of water from the blood plasma to the tissues in a cold environment and from the tissues to the blood plasma in a warm environment is correlated with the regulation of body temperature. In an extensive study of the control of water movement in response to environmental temperature, Barbour (1940) found that in cats transection of the brain stem in the anterior region of the hypothalamus may result in abnormally high osmotic pressure levels with reduction in the specific gravity of the blood. The normal osmotic pressure and specific gravity responses to cold persist only when injury to the hypothalamus involves the rostral portion. The control of osmotic pressure and the specific gravity of the blood therefore seem to be localized in the rostral portion of the hypothalamus, the former involving a somewhat more extensive portion than the latter.

In the monkey osmotic pressure and the specific gravity of the blood also are regulated through the anterior thalamic nuclei, but this animal exhibits the capacity to utilize pathways for vicarious regulation of temperature and water shifting in a remarkable degree. Temperature regulating and osmotic and specific gravity reactions recover within a period of approximately eight days even after complete transection of the brain stem at the level of the roots of the oculomotor nerves.

Fat Metabolism.—Disturbances in fat metabolism have been observed frequently in association with either hypothalamic or hypophyseal lesions. Both these structural entities probably influence this important function. Evaluation of the rôle of each in fat metabolism is rendered even more difficult because of their close proximity to one another and the neural connections of the hypophysis with the hypothalamus.

On the basis of his findings in an extensive study of dystrophia adiposogenitalis, Frohlich (1901) advanced the opinion that this disorder is caused by a hypothalamic lesion. This opinion also is supported by Erdheim (1904, 1916) who found the hypophysis histologically intact in patients with dystrophia adiposogenitalis. On the other hand, he also found this disease associated with hypophyseal tumors. On the basis of his own observations and those of other investigators he concluded that dystrophia adiposogenitalis, when associated with a tumor of the hypophysis, is not

caused by hypophyseal dysfunction but by the effect of the tumor on adjacent parts of the hypothalamus

Evidence of other clinical syndromes which involve disturbances in fat metabolism associated with lesions of the hypothalamus in the absence of lesions of the hypophysis is not wanting (Cushing 1912, Fulton and Bailey 1929, Economo 1931, Lhermitte 1934, Gagel 1936 and others) Marked adiposity due to a hypothalamic lesion usually is associated with a lesion in the region of the tuber cinereum Extreme emaciation sometimes is associated with a lesion of the hypothalamus located farther from the rostral end In some instances adiposity associated with a hypothalamic lesion is followed by emaciation

In an extensive investigation of the serum lipoids in patients with hypothalamic disorders, Gildea and Man (1940) found the fatty acid and cholesterol contents abnormally high in all cases In a similar study in twenty-four patients with hypophyseal disease, they found the lipoid content abnormally high in only five cases

The results of experimental studies, including those of Smith (1927 1931), Keller *et al* (1932, 1936), Crooke and Gilmour (1938), Biggart and Alexander (1939) and Ranson and his collaborators (1938 1939) and others show clearly that in various mammals bilateral lesions in the region of the tuber cinereum which may extend deeply into the hypothalamus but without injury to the hypophysis, may result either in obesity or emaciation Lesions involving both the hypothalamus and the hypophysis also result in disturbances in fat metabolism On the other hand, complete removal of the hypophysis without damage to the hypothalamus does not result in adiposity

The experimental data cited above emphasize the importance of the anterior portion of the hypothalamus in the regulation of fat metabolism but they do not warrant the conclusion that this function is localized in any particular nucleus or group of nuclei As Biggart and Alexander (1939) have pointed out, all lesions causing obesity interrupt some group of fibers The data advanced by Hetherington and Ranson (1940) seem to support the assumption that interruption of longitudinal fibers located in the ventral portion of the hypothalamus is more important in the production of adiposity than interruption of the hypothalamico hypophyseal tract

Animals which have become obese following hypothalamic lesions also exhibit other metabolic disturbances Hetherington and Weil (1940) reported widespread changes in the physiologic economy of the body in rats obese due to hypothalamic lesions Chemical analysis of the tissues showed marked depletion of the supply of both calcium and phosphorus and irregular reduction in the iron content

The mechanism through which the hypothalamic influence in fat metabolism is exerted is not fully understood This influence may be mediated secondarily through the hypophysis or through neural connections with the liver and possibly other glands

Protein Metabolism —The hypothalamus undoubtedly exerts a regulatory influence in protein metabolism, but the mechanism through which this is accomplished as yet is unknown Data bearing on this problem are relatively meager Hypothalamic stimulation apparently inhibits protein metabolism (Leschke and Schneider, 1918), whereas elimination

of the hypothalamic influence by transection of the spinal cord in the cervical region results in its acceleration (Freund and Grafe, 1912, 1913)

Sexual Behavior —Data bearing directly on the influence of the hypothalamus in sexual behavior as yet are meager In certain species the gonadotropic functions of the hypophysis are known to be influenced by impulses emanating from the hypothalamus (Brooks 1940) Hypothalamic mechanisms consequently, must exert an indirect influence in the production of gonadal hormones Sexual behavior undoubtedly depends in large measure on the reactions of central neural mechanisms to these hormonal substances

In certain mammalian species the full pattern of mating behavior can be elicited after complete decortication Component parts of this pattern also can be elicited in animals with the brain stem transected below the diencephalon Evidence of any essential role of the corpus striatum or the major portion of the thalamus in the elaboration of the sexual behavior is wanting Certain experimental data support the assumption that sexual behavior is significantly influenced by hypothalamic neural mechanisms (Bard 1940) but present knowledge does not warrant a precise statement regarding the role of the hypothalamus in the central nervous control of sexual reactions

Emotional Behavior —A significant role of the hypothalamus in emotional expression or at least its outward manifestations, is indicated by the data obtained in many experimental investigations These data however afford no conclusive evidence of actual participation of this division of the brain in emotional experience

As early as 1892 Goltz described signs of rage, in a decorticate dog similar to rage reactions of a normal dog but elicited more easily For example gentle handling of the animal, such as removing it from its cage evoked barking growling and biting Rothmann (1923) reported similar reactions in a decorticate dog Reactions simulating rage in decorticate cats have been reported by various investigators, including Dusser de Barenne (1920) Cannon and Britton (1927) Bard (1928–1934) and others Schaltenbrand and Cobb (1930) reported that one of their decorticate cats "showed different moods" In general the reactions simulating rage in decorticate animals conform to those which Cannon and Britton designated as "sham rage" They are essentially undirected and do not continue after the stimulus has subsided

In an extensive series of experiments on decorticate cats and dogs, Bard and his co-workers (1928–1937) found that sham rage could be elicited regularly after ablation of the corpora striata and the rostral half of the diencephalon Their data seem to warrant the conclusion that the central neural mechanisms which play the major role in these reactions are localized in the caudal portion of the hypothalamus This conclusion also is supported by extensive data reported by other investigators, particularly Ranson and his co-workers

Further evidence that the hypothalamus includes mechanisms involved in emotional expression is afforded by the results of experiments in which this part of the brain stem was stimulated directly Such stimulation in an anesthetized cat elicits parts of the rage reaction In a cat in the waking state it elicits the full emotional response (Kabat *et al*, 1935)

Affective responses in acute decerebrate animals have been reported

particularly by Woodworth and Sherrington (1904) and Keller (1932). They differ from the affective responses of decorticate animals in being less complete. Some reactions involved in affective behavior obviously are mediated through central mechanisms located in lower divisions of the brain stem, but the full expression of reactions such as those of sham rage requires the integrity of hypothalamic mechanisms. In experiments reported by Kessler (1941), cats and monkeys exhibited no spontaneous emotional reactions following total destruction of the hypothalamus, although affective responses could be elicited reflexly.

The emotional changes associated with hypothalamic lesions in man include alternating moods of excitement and depression (Alpers 1937), excessive emotional lability (Dott, 1938), anxiety (Guttman and Herman, 1932, Grinker, 1939) and apathy. The emotional crises of patients with hypothalamic disease are fairly uniform despite their premorbid emotional make-up (Alpers, 1940). The clinical data available do not warrant the conclusion that the hypothalamus is the chief center of emotional expression but clearly indicate that it plays a significant role in emotional behavior and that hypothalamic disease not uncommonly results in emotional disturbances.

Sleep and the Waking State.—Patients with hypothalamic tumors not infrequently exhibit somnolence in a marked degree. The results of studies of encephalitis lethargica, particularly those of von Economo (1930), also afford evidence of the subcortical regulation of sleep. This investigator reported cases in which somnolence was associated with inflammation of the gray matter at the junction of the diencephalon and mesencephalon, and cases in which initial choreic unrest and tormenting insomnia were associated with lesions located more rostrally in the walls of the third ventricle. The results of other clinical studies, many of which have been reviewed by Harrison (1940), afford further evidence of the importance of hypothalamic mechanisms in the regulation of sleep.

The results of animal experimentation also support the assumption that the hypothalamus includes important sleep regulating mechanisms. Some of the most significant experimental data have been reported by Ranson and Ingram (1932), Ingram, Barris and Ranson (1936) and Ranson (1939). These data and those reported by various other investigators have been critically analyzed by Ranson and Magoun (1939). On the basis of the data analyzed it is evident that bilateral lesions in the caudal portion of the lateral hypothalamic region result in somnolence most consistently. Lesions in the central gray matter or other parts of the hypothalamus which do not involve the lateral hypothalamic regions usually are not accompanied by somnolence. Data reported by Harrison (1940) indicate that even very small bilateral lesions accurately placed in the lateral hypothalamic region consistently result in somnolence in a marked degree.

Since decortication results in increased excitability and direct stimulation of the hypothalamus elicits intense excitement, whereas appropriately placed bilateral hypothalamic lesions result in somnolence it seems reasonable to assume that somnolence results from suppression of hypothalamic activity and that, under normal conditions, the hypothalamic drive exerting its influence on lower neural centers is an important factor in maintaining the waking state. Elimination of this influence results in relaxation of the body and thus favors sleep. The central mechanisms

through which the sleep-waking rhythm is regulated therefore do not constitute a "sleep center" but, as has been pointed out by Ranson (1940), a region the integrity of which is required for maintaining the waking state.

General Visceral Functions.—The regulatory influence of the hypothalamus in the various bodily functions referred to above is exerted mainly on visceral organs but in part also on somatic tissues. Since the efferent innervation of the visceral organs is solely autonomic, impulses emanating from the hypothalamus reach them only through the autonomic nerves. The somatic tissues receive hypothalamic impulses directly through extrapyramidal somatic efferent conduction pathways. Somatic tissues may also be influenced through hormonal agents liberated in consequence of autonomic stimulation. Respiration may be regarded as a general visceral function which involves extensive somatic neuromuscular mechanisms as well as the autonomic innervation of the respiratory tract.

The functional regulation of the cardiovascular system, under normal physiologic conditions, is mediated mainly through centers in the medulla oblongata. These mechanisms are subject to regulatory influences from higher centers and probably require such influence, particularly from the hypothalamus, for the adequate adjustment of the blood flow under various conditions of bodily activity and external temperature.

Experimental evidence of the capacity of the hypothalamus to influence cardiovascular function is not wanting. Electrical stimulation of the hypothalamus may cause a rise in blood pressure or a fall depending on the location of the electrodes (Karplus and Kreidl, 1918; Kabat, Magoun and Ranson, 1935; Hare and Geohegan, 1939). Localized heating of the hypothalamus results in vasodilatation, localized cooling in vasoconstriction (Barbour, 1912; Magoun, Harrison, Brobeck and Ranson, 1938). The magnitude of the effect of impulses emanating from the hypothalamus on the cardiovascular centers in the medulla oblongata is conditioned by other influences acting on these centers at the moment, such as afferent impulses from the aorta and the carotid sinuses. The hypothalamic influence is decreased during concurrent afferent stimulation from these sources and increased during afferent stimulation which tends to excite the vasomotor centers to produce a rise in blood pressure. Conversely, the effect of afferent stimulation on cardiovascular centers may be modified by impulses from the hypothalamus. Afferent impulses from the carotid sinuses and the aorta inhibit the discharge of efferent impulses through the cardiac accelerator and vasoconstrictor nerves less effectively during a concurrent discharge of excitatory impulses from the hypothalamus, whereas the effect of peripheral afferent stimulation is increased. Hypothalamic activity, therefore, may either augment or decrease the effectiveness of afferent impulses in the reflex regulation of the cardiovascular system (Bronk, Pitts and Larrabee, 1940).

Cardiovascular responses to hypothalamic stimulation commonly are accompanied by responses in other visceral organs. Appropriate stimulation of the hypothalamus in an anesthetized animal results in increased blood pressure due to contraction of the smaller arteries and arterioles, dilatation of the pupils, acceleration of the respiratory movements and increased depth of respiration, increased tonus of the musculature of the urinary bladder, etc. Dilatation of the pupils and contraction of the vas

cular musculature are mediated through sympathetic nerves, contraction of the bladder musculature is mediated through parasympathetic nerves Both these responses are frequently associated with acceleration and increase in depth of respiration during hypothalamic stimulation

The particular combination of responses elicited by stimulation of the hypothalamus is determined in a large measure by localization of the stimulus Contractions of the urinary bladder associated with a decrease in the rate and depth of respiration, sometimes accompanied by a decrease in blood pressure and retardation of the cardiac rhythm, may be elicited in cats by direct stimulation in the region just in front of the hypothalamus (Ranson, 1940) These results support the assumption that impulses emanating from the rostral portion of the hypothalamus reach the visceral organs mainly via the parasympathetic nerves Stimulation of the hypothalamus farther from the rostral border commonly elicits visceral responses mediated through sympathetic nerves, *e g*, inhibition of gastrointestinal motility and acceleration of cardiac rhythm, but may also result in contraction of the urinary bladder or other parasympathetic responses due to stimulation of descending pathways arising in centers the stimulation of which normally elicits parasympathetic responses In general the regulatory influence of the hypothalamus on the visceral organs which is mediated through the parasympathetic nerves seems to emanate from the rostral portion and that which is mediated through the sympathetic nerves from the more caudal portions, including the lateral hypothalamic regions

Fragmentary observations on the autonomic reactions elicited by direct stimulation of the hypothalamus in man indicate that they are comparable to those observed in experimental animals As reported by White (1940), electrical stimulation, under local anesthesia, of the wall of the third ventricle in the region of the paraventricular nucleus elicited abrupt acceleration of the cardiac rhythm and a rise in blood pressure in five conscious patients Similar stimulation in the region of the preoptic nucleus resulted in retardation of the cardiac rhythm in one patient Operative manipulation in this region regularly resulted in sudden bradycardia in seven conscious patients but no retardation of the cardiac rhythm in patients under atropine or ether anesthesia Of eight patients in whom stimulation or operative manipulation of the hypothalamus resulted in bradycardia four exhibited abrupt depression in the level of consciousness ranging from drowsiness to coma

Hypophyseal Function—The various hypophyseal hormones play a significant role in the regulation of visceral functions both through their neurogenic effects and their direct influence on the activities of other endocrine glands The hypothalamic influence exerted on the pars nervosa of the hypophysis through the hypothalamo-hypophyseal tract is discussed in a preceding section (see p 90) The fibers of this tract terminate mainly in the pars nervosa, but presumptive evidence that nerve impulses conducted through it also reach the pars anterior is not wanting, since Brooks (1938), Hair (1938) and Rasmussen (1938) have traced some fibers of hypothalamic origin into the anterior hypophyseal lobe In man, according to Rasmussen, the number of these fibers is negligible

The pars anterior of the hypophysis seems to have a basic secretory rhythm which is regulated mainly through hormonal products of peripheral endocrine glands Under certain environmental conditions this

rhythm may be modified by impulses which reach the hypophysis through the hypothalamo-hypophyseal tract and, probably to a lesser extent through the cervical sympathetic nerves. The production particularly of the thyrotropic and gonadotropic hormones is known to be influenced through these conduction pathways (Lotila, 1940). The hypothalamic regulation of these hormones may be of considerable biological significance since it provides for hypothalamic regulation of certain autonomic functions through the hypophysis as well as through the peripheral autonomic nerves.

Cortical Regulation of Autonomic Functions.—Among the early investigators who recognized cortical participation in the regulation of visceral functions may be mentioned, Schiff (1875), Danilewsky (1875), Bochefontaine (1876), Bechterew and Mislawski (1886), Stricker (1886), Winkler (1898) and others. They detected cortical influences exerted through the autonomic nerves mainly on the cardiovascular system. The results of numerous more recent investigations have revealed cortical influence in the regulation of all visceral functions. The concept of general autonomic representation in the cerebral cortex now rests on the results of many experimental studies involving both stimulation and ablation of cortical areas in animals including primates, and abundant clinical observations. The literature bearing on this problem has become too voluminous to be reviewed in detail in this connection. It has been summarized particularly by Fulton (1936, 1943) and Kennard (1937).

The cortical regions involved in the regulation of autonomic functions include mainly the motor and premotor areas, particularly areas 4 and 6 of Brodmann, although visceral effects of stimulation of certain other areas have been reported (Baily and Sweet, 1940). There is therefore extensive overlapping of the areas involved in autonomic and somatic motor functions, making possible a high degree of correlation between visceral and somatic reactions. The areas which are chiefly concerned in the cortical regulation of specific visceral functions probably are closely related to the cortical areas through which corresponding somatic functions are regulated (Spiegel, 1928). For example, stimulation of the motor area for the face and tongue elicits salivation, and stimulation of the motor eye fields elicits lacrimation. The autonomic responses to localized cortical stimulation are less definitely circumscribed than the somatic responses, since stimulation at a single point may result in a widespread discharge through the autonomic nerves. There are no circumscribed cortical areas for sympathetic and parasympathetic reactions respectively, but the character of the autonomic response to stimulation of any appropriate cortical area seems to be determined by the physiological state of the animal and the physiological state of the cortex at the time of stimulation (Crouch and Thompson, 1939).

The mechanisms through which impulses emanating from the cerebral cortex influence visceral functions as yet are not fully known. The fibers of cortical origin through which these impulses are conducted probably terminate mainly in the diencephalon and at lower levels in the brain stem. Much of the cortical influence undoubtedly is exerted through the hypothalamus. Some of the available data, particularly those which indicate exaggerated autonomic activity following cortical ablation, support the assumption that the influence of the cerebral cortex on visceral function

is predominantly inhibitory Direct stimulation of the cortex in intact animals sometimes elicits autonomic activation but more commonly autonomic inhibition The exaggerated autonomic activity commonly observed following cortical lesions obviously indicates the release of the autonomic centers in question from the inhibitory influence of the cortex

Particular cerebral states influence visceral functions more or less specifically For example grief not uncommonly results in depression of the general metabolic functions and activation of the lacrimal glands States of perplexity or fright commonly result in generalized sympathetic stimulation Every emotional state probably results in vasomotor manifestations which not infrequently are highly specific Worry commonly is accompanied by peripheral vasoconstriction joy by peripheral vasodilatation shame by an irregular distribution of peripheral vasodilatation Such visceral reactions to cerebral states also have their counterparts in somatic reactions For example, pleasurable emotions are reflected in the buoyant postures and movements of the body Grief, on the other hand, is reflected in drooping postures and slow movements Strong emotions may result in temporary loss of muscular control under certain conditions and the ability to exert extraordinary muscular effort under other conditions These somatic responses undoubtedly are closely correlated with the visceral responses associated with the same cerebral states

CHAPTER V

GENERAL PHYSIOLOGY (CONTINUED)

The Autonomic Nervous System in Relation to the Endocrine Glands — Functional interdependence of the autonomic nervous system and endocrine glands is demonstrated by many physiological phenomena. This relationship is deep seated and may be regarded as a result of long-continued evolutionary processes. The most primitive forms of animal life respond mainly to chemical stimuli. These responses are inadequate to meet the needs of higher animals. The development of a nervous system through which rapid conduction and widespread coordination can be accomplished is a comparatively late event in evolution. In all the higher animals, reactions to environmental factors as well as the regulatory control of the internal organs are dominated by the nervous system but chemical stimulants play an important role in the functional regulation of the internal organs. As differentiation advanced the chemical stimulants became concentrated and specialized in the ductless glands and there arose a reciprocal relationship between these glands and the innervation of the internal organs through which a delicate balance of the vital functions is maintained. The first purpose for which rapid conduction and coordination became vital is self preservation. By virtue of the wide distribution of efferent impulses made possible by the synaptic connections of a single preganglionic fiber with many ganglionic neurons, and the chemical mediation of nerve impulses, particularly at the neuro-effector junctions (see p. 104), the autonomic nervous system is adapted for rapid and widespread reactions. In these reactions the autonomic nerves stimulate the secretion of the endocrine glands. These secretions in turn augment the responses called forth through the autonomic nerves.

The Adrenals—Langley's generalization that the effect of adrenin on any part of the body is the same as the effect of stimulation of its sympathetic nerves, expresses one of the fundamental reciprocal relationships of nervous and chemical stimuli. Although there are certain exceptions to this generalization, it may be stated that sympathetic stimulation commonly excites the secretion of adrenin and adrenin increases reactivity of the sympathetic nerves to stimulation.

Not a few investigators have observed an increase in the amount of adrenin in the circulation due to sympathetic stimulation. Cannon and de la Paz (1911) reported an increase in the adrenin output due to emotional stimulation. This observation has since been corroborated repeatedly, particularly by Cannon and his associates. The influence of adrenin on the resistance of voluntary muscle to fatigue has long been known (Oliver and Schaefer 1895). According to Gruber (1913) adrenin does not lower the threshold of stimulation for normal muscle but promptly increases the irritability of fatigued muscle, even when a rise in blood pressure is prevented. Adrenin also plays an essential role in calling forth stored carbohydrate, thus increasing the sugar content of the blood. It also plays a part in distributing the blood to the heart, lungs, central nervous system and limbs and in reducing the supply to the abdominal organs while

the latter are inhibited (Cannon, 1915) These facts, according to Cannon, "are associated with some of the most primitive experiences in the life of higher organisms, experiences common to all, both man and beast, the elementary experiences of pain, fear and rage, that come suddenly in critical emergencies" Stewart and Rogoff (1916, 1917), on the contrary, found no conclusive evidence that adrenin is brought into play in a marked degree by emotional stresses or physical strains

In a study of the influence of motion and emotion on adrenin secretion, Cannon and Britton (1927) confirmed the conclusion, based on the results of earlier studies of Cannon and his associates that muscular activity and emotional excitement increase the output of adrenin Taking the increased rate of the denervated heart as a rough measure of the increase of adrenin in the blood, they found that the output of adrenin was increased by even minor bodily movements Extending the limbs or turning the body of a cat with denervated heart, in their experiments, was accompanied by an increase in the heart-rate of 5 to 10 beats per minute Walking increased the rate 10 to 20 beats When the adrenal glands were inactivated, the same activities were accompanied by but slight acceleration of the heart or none at all Emotional excitement resulted in an even greater increase in the rate of the denervated heart The same excitement of the same animals, following inactivation of the adrenal glands, resulted in but slight cardiac acceleration or no change in rate Great emotional excitement plus vigorous activity, in cats with denervated heart, caused an increase in the heart-rate of 30 to 80 beats per minute while the adrenals were intact but usually only 8 beats or less following inactivation of the adrenal glands In view of these results, they suggested that "the increased secretion of adrenin accompanying incidental and routine muscular movements such as walking its greater concentration in the blood during muscular exercise and its abundant outpouring as a consequence of vigorous struggle emphasize the probable significance of adrenin for efficient use of muscles in the body "

The finding that even slight muscular exertion calls forth increased production of adrenin might seem to be incompatible with the emergency theory previously advocated by Cannon and his associates It seems to indicate that what takes place on a large scale in emergencies takes place on a smaller scale in the ordinary behavior of the organism Cannon and Britton, therefore, suggested that "the emergency theory would have to be altered insofar as it might imply that the sympathico-adrenal mechanism is called into action only at times of violent emotion According to the evidence now in hand, the greater the emergency, as measured by intensity of excitement and struggle, the more is that mechanism utilized "

Persistence of the visceral concomitants of emotional excitement for some time after the stimulus has ceased to act is a fact of common experience In the experiments of Cannon and Britton, this was attributed solely to continued adrenal secretion According to these authors, "this extension of the visceral disturbances in time has a bearing on conduct in an exciting situation, as well as thereafter It points out the natural effect of the full expression of fear or rage, and shows the importance of limiting that expression if a persistent state of disquiet is to be avoided It also corroborates the counsel that when bodily functions are dominated by sympathetic influences, as in the more powerful emotions, the exercise

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of opposed functions should not be attempted Thus, the digestive processes, which are inhibited by excitement, may continue to be disturbed for a considerable period, and digestion cannot proceed properly until a state of calm has been restored"

An augmenting effect of adrenin on the discharge of glycogen from muscle tissue has been demonstrated by Corkill, Marks and Soskin (1935) The amount discharged due to large doses of adrenin, in their experiments, was approximately double the amount discharged due to sympathetic stimulation The finding that administration of adrenin effectively augments the discharge of glycogen from skeletal muscles supports the assumption that the discharge due to sympathetic stimulation is mediated through the adrenin like substance, sympathin liberated as a result of stimulation of sympathetic nerves

Intensification of the effect of sympathetic stimulation on the nictitating membrane of the cat by secreted adrenin has been demonstrated by Rosenblueth and Cannon (1932) and by injected adrenin by Rosenblueth and Rioch (1933) Summation of the effects of sympathetic nerve impulses, adrenin and sympathin also has been demonstrated by Liu (1935)

Although the commonly observed effect of the injection of adrenin on the vasomotor mechanism is a rise in blood pressure, it has long been known that the injection of adrenin in high dilutions under certain conditions may result in a fall in blood pressure (Moore and Purinton, 1900) Elimination of the normal output of adrenin by ligation of the adrenal vessels does not necessarily result in an appreciable fall in blood pressure for a period of at least several hours as should be expected if the sympathetic nerves were kept in tonus by adrenin (Young and Lehman, 1908, Hoskins and McClure 1912) In certain animals (cats and dogs), the administration of adrenin in appropriate dosage may result in inhibition of gastro intestinal peristalsis without causing a rise in blood pressure (Hoskins and McClure 1912, Durant 1925)

If the blood pressure were maintained by a constant minimal discharge of adrenin as has been assumed by many, any increase in the quantity of this substance should result in a rise in blood pressure Very dilute solutions may be injected without any effect on blood pressure Hoskins and McClure (1912) reported that when the rate of injection of such a dilute solution is increased, the threshold of stimulation is reached and the blood pressure instead of rising, falls On the basis of this observation, they advanced the opinion that if the adrenals exert a constant effect by continuous secretion of adrenin it must be a depressor effect In another series of experiments Hoskins (1915) found that the slow infusion of adrenin into the blood stream of an adrenalectomized dog resulted not in increased sympathetic irritability, as indicated by the reaction to nicotine but an actual decrease in sympathetic reactivity This finding was corroborated by Hoskins and Rowley (1915) in a relatively large series of dogs

On the basis of the above findings and other experimental data, Hoskins (1927) advanced the opinion that adrenin "consistently and generally exerts a biphasic effect as it has been shown to do in cases of intestinal peristalsis, uterine contractions and blood vessels in muscles In that case it would serve, under ordinary conditions if present at all as a sympathetic sedative as does calcium another normal constituent of the blood Under other conditions its stimulating effect would come into play"

Although this view may seem paradoxical, it is not incompatible with the experimental data which indicate only a stimulating effect of adrenin It also conforms precisely to Verworn's theory that inhibition is due to subminimal stimulation Inhibitory effects of adrenin on reactions mediated through sympathetic nerves, under experimental conditions, have been reported also by other investigators Malmejac, Donnet and Desanti (1935) observed diminished adrenin secretion due to injection of adrenin Hsu and Chu (1937-1938) reported central inhibitory effects of adrenin demonstrated by dilatation of the independently perfused spleen and diminution of the pressor response to stimulation of the floor of the fourth ventricle Heymans *et al* (1937) reported vasodilatation of the independently perfused kidney and extremities following injection of adrenin Marrazzi (1939) reported an inhibitory effect of adrenin on the transmission of impulses through sympathetic ganglia On the basis of results obtained in a series of experiments carried out on cats under urethane and chloralosane anesthesia, Darrow and Gellhorn (1939) advanced the conclusion that adrenin either secreted or injected results in diminished reflex excitability of the sympathetic nerves

Some of the observed reactions on which this conclusion is based probably can be explained most satisfactorily on the basis of the known inhibitory effects of adrenin on cholinergic mechanisms For example Bain, Irving and McSwiney (1935) and Ury and Gellhorn (1939) have shown that the reflex inhibition of parasympathetic tonus in the reflex dilatation of the pupil elicited by afferent nerve stimulation is increased by the presence of adrenin The inhibitory effects of reflex stimulation on the parasympathetically innervated sympathectomized pupil also are increased and the secretory activity of the normally innervated sweat glands is diminished (Darrow and Gellhorn, 1939) The inhibitory effects of adrenin on adrenergic sympathetic mechanisms, therefore may be due at least in part to its effect on the transmission of impulses through the ganglia, which involves an acetylcholine-like mediator

The Thyroid Gland —Functional interrelationships of the thyroid gland and the autonomic nervous system, including the hypothalamic autonomic centers, has been amply demonstrated but the mechanisms through which the thyroid is influenced by autonomic nerve impulses and those through which the thyroid influences autonomic nerve activity are not fully known Certain anatomical data support the assumption that sympathetic nerve fibers actually effect functional contacts with thyroid cells but there is no complete agreement on this point Thyroid activity is known to be influenced by stimulation of the cervical sympathetic nerves It also is subject to hypothalamic influences by virtue of the effect of impulses emanating from the hypothalamus on the production of the thyrotropic hormone in the anterior lobe of the hypophysis The integrity of either the peripheral autonomic nerves or the hypothalamo-hypophyseal tract is not essential for continued thyroid function but the response of the thyroid to certain conditions of stress, such as exposure to cold, is impaired following bilateral extirpation of the cervical portion of the sympathetic trunk and completely abolished following section of the hypophyseal stalk (Uotila, 1939) The thyrotropic activity of the hypophysis also is influenced by thyroxin produced in the thyroid gland This influence seems to be exerted via the hypothalamus (Lichtwitz, 1936)

Compensatory hypertrophy of the thyroid tissue following subtotal thyroidectomy is diminished in animals in which the hypophyseal stalk has been sectioned as compared with that which takes place in normal control animals (Uotila, 1940) Under normal physiological conditions the thyrotropic hormone undoubtedly plays a more significant role in the regulation of thyroid function than impulses conducted through the cervical sympathetic nerves, except in as far as the latter regulate the flow of blood through the thyroid

The influence of the thyroid on metabolism involves the activity of other endocrine glands, particularly the adrenals, as well as the autonomic nerves Stimulation of the cervical sympathetic nerves does not consistently alter the basal metabolic rate (Brock *et al* 1940) Bilateral extirpation of the cervical portion of the sympathetic trunk, in cats and rabbits, quite consistently results in depression of the basal metabolic rate (Friedgood and Cannon, 1940, Brock *et al*, 1940) In experiments reported by Asher and Ruetsch (1940), threshold doses of adrenin gave rise to increased muscle temperature, in rabbits, as measured thermo-electrically Following denervation of the thyroid the same rise in muscle temperature could be obtained only with larger doses of adrenin acting for a longer time In experiments reported by Mahoney and Sheehan (1936), the basal metabolic rate remained unaltered in monkeys following section of the hypophyseal stalk

Lieb and Hyman (1922) have shown that repeated injections of adrenin in experimental animals increasingly augment the irritability of the sympathetic nerves, regardless of the functional condition of the thyroid gland In experiments carried out by Hoskins (Hoskins and Lee, 1930), thyroidectomy seemed to produce varying effects on the sympathetic and parasympathetic divisions of the autonomic nervous system in the various experimental animals used Certain data reported by Bergwall and Kuschinsky (1931) are more significant In their experiments, thyrotoxicosis induced by the administration of thyroxin resulted in sympathetic hyperirritability due to an increased output of adrenin, *i e*, thyroxin poisoning resulted in increased secretory activity of the adrenal glands These results strongly suggest that the effect of the thyroid secretion on sympathetic irritability, particularly under conditions of hyperthyroidism in reality is the result of its stimulating effect on the adrenal glands Certain data advanced by Oberdisse (1931) indicate that thyroxin in the circulating blood also exerts a direct effect on the tissue elements Small non-toxic doses of thyroxin, according to Kalnins (1928), sensitize the parasympathetic nerve endings in the intestine

The results of clinical studies reported by MacLean, Horton and Davis (1938) also support the assumption that thyroid hyperactivity results in increased parasympathetic tonus In hyperthyroid states, according to their findings the cholinergic nerves are stimulated directly and not the adrenergic Symptoms associated with hyperthyroidism which have commonly been regarded as evidence of sympathetic stimulation, such as increased cardiac rhythm, probably can be explained more satisfactorily as compensatory phenomena or as due to a nicotine-like action of thyroxin on the synapses Hypothyroidism not uncommonly results in hypoactivity of the cholinergic nerves as indicated by reduced secretory activity of the sweat glands

The Parathyroid Glands —The fact that parathyroid deficiency results in generalized neuromuscular hyperirritability suggests a functional interrelationship between these glands and the sympathetic division of the autonomic nervous system Experimental proof of this interrelationship also is at hand In experiments reported by Hoskins and Wheelon (1914) dogs which had developed typical parathyroid tetany, following extirpation of the parathyroid glands, gave unmistakable evidence of increased sympathetic irritability in their reactions both to adrenin and nicotine

The Pancreas —The internal secretion of the pancreas seems to exert a definite influence on the parasympathetic nerves, but probably exerts no direct effect on the sympathetic nerves (Hoskins and Gunning, 1916) According to Santenoise and Tinel (1923) and Garrelon and Santenoise (1924), the cardiac and respiration rates are decreased and the susceptibility to shock is increased following the injection of insulin That these effects were not the results of hypoglycemia, in their experiments, is indicated by their occurrence also when glucose was administered simultaneously with the insulin Other typical reactions of clinical patients and experimental animals following large doses of insulin and before the symptoms of hypoglycemic convulsions appear, *e g*, salivation and exaggerated contractions of the stomach and intestine, also indicate increased parasympathetic irritability

The Hypophysis —The dependence of certain of the functions of the pars nervosa of the hypophysis on impulses emanating from the hypothalamus is evidenced by the effects of hypothalamic lesions or interruption of the hypothalamo hypophyseal tract particularly on carbohydrate and water metabolism outlined above (See p 89) Certain of the hormones produced in the pars nervosa also influence autonomic nerve functions

The effect of pituitrin on the contractions of smooth muscle is well known Certain data seem to indicate that the sympathetic nerves may be sensitized to adrenin by the injection of hypophyseal extracts even in small doses (Kepinow, 1912) Certain other data fail to support this assumption (Hoskins and Lee, 1930) A direct action of posterior hypophyseal hormones on the autonomic nerves has not been demonstrated beyond question but may be inferred from the antagonistic effects of posterior hypophyseal extract and insulin The administration of posterior hypophyseal extract tends to bring about hyperglycemia or reduce the hypoglycemia resulting from the administration of insulin (Burn, 1923, Lawrence and Hewlett, 1925, Heymans and Pupeo 1926) Since insulin must be regarded as a parasympathetic stimulant, these facts suggest that the posterior hypophyseal secretion includes a sympathetic stimulant The fact that posterior hypophyseal hormones augment basal metabolism and the mobilization of sugar also supports this assumption

The assumption that impulses emanating from the hypothalamus play a rôle in the functional regulation of the pars distalis of the hypophysis is supported by both clinical and experimental data Appropriate electrical stimulation of the hypothalamus results in the release of gonadotropic hormone from the anterior hypophyseal lobe (Marshall and Verney, 1936, Harris, 1937, Haterius, 1937) Section of the hypophyseal stalk also results in slight disturbances of anterior hypophyseal functions (Brooks, 1938, Dempsey, 1939) Cytological changes in the anterior lobe following stalk section have been reported (Brooks, 1938, Uotila, 1939) but identical

changes also have been observed following thyroidectomy and after injections of thyroxin or œstrin (Uotila, 1940). The regulatory control of the anterior lobe is mediated mainly through hormonal substances but its functional rhythm may be modified due to certain environmental situations, by impulses which reach it via the hypophyseal stalk or, to a lesser extent, through the cervical sympathetic nerves.

The Gonads.—The assumption that there is a special functional interrelationship between the ovaries and the autonomic nerves, although long prevalent, is supported by little direct evidence. It rests mainly on the presumption that the well-known vasomotor instability which often arises at the climacteric is due to the subsidence of the ovarian hormones. This presumption finds some support in the fact that the vasomotor instability in question, in many instances, has been ameliorated by the administration of ovarian preparations. On the experimental side Hoskins and Wheelon (1914) reported that the responses to sympathetic stimulation were materially increased in dogs following removal of the ovaries.

During every cycle in the activity of the female reproductive system there is a phase of relatively slow growth of the uterine mucosa during which the basal metabolism remains at a more or less constant low level, and a phase during which the basal metabolic rate is higher. The former phase seems to be dominated by the activity of the corpus luteum. The latter is initiated with the regression of the corpus luteum. In the rat, according to Lee (1928), the maximum difference in the basal metabolic rates during the two phases approximates 12 to 15 per cent. If the assumption that the parasympathetic system subserves conservative functions be correct, it may be assumed that the corpus luteum acts synergistically with the parasympathetic nerves.

That extirpation of the male sex glands results in some degree of depression is assumed quite commonly, although there is little clear-cut evidence in favor of this assumption. The results of quantitative studies on rats reported by Hoskins (1925) and Richter and Wislocki (1928) show that castration actually results in three- to four-fold psychomotor retardation. The direct effect of castration on either division of the autonomic system is not brought out by the results of these studies. The results of experiments carried out on dogs, previously reported by Wheelon (1914, 1916), show clearly that the sympathetic nerves become materially less sensitive to stimulation following castration and that sympathetic irritability in a large measure is restored following successful testicular grafts.

Chemical Mediation of Autonomic Nerve Impulses.—The Chemical Mediators.—The concept of chemical mediation of nerve impulses, although relatively new, is based on the results of numerous experimental studies. The humoral substances are liberated at the neuro-effector junctions or near them as well as at the synaptic junctions in the autonomic ganglia and within the central nervous system.

The possibility of chemical mediation of nerve impulses was suggested by the pioneer work of Elliott (1905) on medulli-adrenal secretion. Little progress was made in this field until Loewi (1921) reported the results of experiments on frogs in which he demonstrated that a perfusion fluid passing through the heart acquires a new property depending on the character of the nerve impulses dominating the heart at the moment. This new property was indicated by the effect of the perfusion fluid on a second

frog's heart through which it was passed in the absence of nerve stimulation. When the first heart was under the influence of sympathetic stimulation, the second also was accelerated; when the first was under the influence of parasympathetic stimulation, the second also was inhibited, i. e., the perfusion fluid acquired the capacity to transmit to the second heart the effect of the nervous stimulation of the first prevailing at the moment. The substances liberated into the circulating medium by which these effects are brought about also exert the typical sympathetic and parasympathetic effects respectively on other visceral organs (Brinkman and van Dam, 1922). Finkelman (1930) reported that Ringer's solution allowed to flow over a pulsating piece of rabbit's intestine, still supplied with its mesenteric nerves, acquires a new property when the nerves are stimulated which may be demonstrated by allowing the solution to flow over a second piece of pulsating intestine. If the first piece is inhibited by sympathetic stimulation, the second piece also is inhibited by the action of the Ringer's solution flowing over it. In experiments on the perfused tongue of the dog reported by Bain (1932, 1933), stimulation of the sympathetic nerves resulted in the addition to the perfusion liquid of a substance which, when transmitted humorally to an isolated strip of rabbit's intestine, caused a decrease in the tonus or contractions of the muscle. Stimulation of the parasympathetic nerves, on the other hand, resulted in the addition to the perfusion liquid of a substance which, when similarly transmitted to an isolated strip of rabbit's intestine, caused augmentation of the tonus or contractions of the muscle. In experiments in which the heart and adrenal glands have been denervated and the spinal cord severed in the cervical region, according to Bacq and Brouha (1932), peripheral stimulation of the sciatic or brachial nerves regularly is followed by acceleration of the cardiac rhythm, due to the direct action on the heart of a substance which is liberated at the periphery, by reason of nerve impulses set up in the postganglionic sympathetic fibers, and reaches the heart through the circulating blood. Stimulation of the hepatic nerves or the abdominal sympathetic trunks, according to Rosenblueth and Phillips (1932) also results in the liberation of a sympathomimetic substance which elicits responses in the denervated heart. Stimulation of the chorda tympani according to Gibbs and Szeloczey (1932) results in the liberation in the submaxillary gland of a parasympathomimetic substance. This substance when injected into the artery supplying the submaxillary gland, in their experiments, acted as a powerful secretory stimulant. It also depressed the isolated heart and stimulated the isolated intestine.

In an experimental investigation reported by Kibjakow (1933), in which the superior cervical sympathetic ganglion was perfused with Locke-Ringer solution, stimulation of the cervical sympathetic trunk resulted in the appearance in the outflowing liquid of a substance which, when injected into the liquid flowing through the superior cervical sympathetic ganglion of another animal, elicited contraction of the nictitating membrane. Experimental data reported by Feldberg and Gaddum (1933) also indicate that stimulation of the cervical sympathetic trunk results in the liberation of a substance in the superior cervical sympathetic ganglion which has the property of activating ganglion cells.

In an experimental investigation involving section of the cervical sympathetic trunk and regeneration of the preganglionic fibers to the

superior cervical ganglion, Brucke (1931) observed apparently normal function of the ocular muscles when only a small number of regenerating fibers had effected synaptic connections in the superior cervical ganglion. In a series of experiments carried out on cats in which the effects of nerve stimulation on smooth and skeletal muscles following section of varying fractions of the nerve fibers were observed, Rosenblueth and Rioch (1933) found, in the case of smooth muscles, that with certain limitations, stimulation of only a small fraction of the nerve fibers involved results in contraction of all the muscle fibers, whereas in the case of skeletal muscles only a part of the muscle contracts in response to stimulation of a fraction of the nerve fibers. They explained this result in smooth muscle on the assumption that a chemical mediator liberated at the sites of the synapses of the intact preganglionic fibers diffused throughout the ganglion and activated other ganglion cells as well as those with which the preganglionic fibers stimulated actually effected synaptic connections.

Rosenblueth (1934) reported certain experimental data which support the assumption that chemical mediators also play a role in the transmission of nerve impulses in central autonomic reflex centers. On the basis of the reflex changes in the cardiac rhythm elicited by afferent maximal stimulation at varying frequencies of the depressor, the left vagus and the sciatic nerve in cats with either the vagi or accelerators severed, he advanced the following hypothesis: "Nerve impulses impinging on a neuron give rise to *quanta* of excitatory (e.c.s.) or inhibitory (c.i.s.) substances according to the differentiated structures within the cell on which they act. Both e.c.s. and c.i.s. are destroyed at a rate proportional to the concentration. For a steady input and at equilibrium the concentrations of e.c.s. and c.i.s. are proportional to the rate of bombardment of the neuron by nerve impulses. C.e.s. attains supraliminal values, thus explains after discharge. The rate of discharge of impulses by the neuron is proportional to the concentration of e.c.s. The output from a center is, therefore, proportional to the excitatory input. C.i.s. combines with e.c.s. inactivating the latter."

The chemical mediator liberated at the periphery in response to sympathetic stimulation exhibits properties similar to those of adrenin. Like adrenin, it becomes inactive when mixed with eosin and exposed to ultraviolet light (Loewi and Navratil, 1926). Like adrenin, it also is rendered more effective by a dilute solution of glycocoll and loses its activity when exposed to air for twenty hours or on being heated to 100° C. (Lanz, 1928). It may be identical with adrenin but, since it is produced under the influence of sympathetic stimulation in tissues other than the adrenal medulla and other chromaffin cells, Cannon (1931) suggested that it be called "sympathin." That sympathin and adrenin are cooperative has been demonstrated by Rosenblueth and Cannon (1931). Having demonstrated the threshold stimuli for sympathin and medulli-adrenal secretion respectively, using the nictitating membrane as an indicator, they found that the simultaneous discharge of both sympathin and adrenin by means of the threshold stimuli, produced a greatly augmented contraction of the nictitating membrane. Cannon (1931) also advanced experimental data in support of the theory that the chemical mediator liberated by sympathetic stimulation enters the blood stream and is carried to distant organs in the circulating blood. According to his account, stimulation of the sympathetic fibers distributed to the erector pili muscles in the tail caused a slow increase

of blood pressure and heart-rate which reached its maximum in two or three minutes and then gradually returned to the former level, in a preparation in which the heart was denervated and the adrenals and liver were excluded from action

The results of certain experiments reported by Cannon and Rosenblueth (1932) have led them to conclude that there are two kinds of sympathin one kind which is liberated in smooth muscle while contracting in response to sympathetic stimulation, and another which is liberated in smooth muscle which is inhibited by sympathetic stimulation They have designated the former sympathin E, and the latter sympathin I Sympathin E, carried in the circulating blood, causes contraction of distant smooth muscle which normally contracts in response to sympathetic stimulation, sympathin I inhibits smooth muscle which normally is inhibited by sympathetic stimulation

Rosenblueth (1932) has reported certain data which seem to support the hypothesis that every quantal autonomic nerve impulse results in the liberation of a quantal amount of chemical mediator substance, consequently, the concentration of this substance depends on the frequency of the nerve impulses Since its destruction takes place at a limited rate, it may diffuse to other structures whenever its concentration exceeds this limit He further advanced the hypothesis that the substance in question combines with some substance in the effector and that the response is proportional to the concentration of the combined substances

Loewi designated the chemical substance liberated in the frog s heart, in his original experiments, the "vagus substance " Inasmuch as stimulation of other parasympathetic nerves also results in the liberation of a parasympathomimetic substance, the term parasympathin proposed by Engelhart would be both more inclusive and more appropriate This substance closely resembles acetylcholine and probably is identical with it Dale and Feldberg (1933) have shown that the substance liberated in the gastric musculature, as a result of vagus stimulation, possesses "all the properties of an unstable, atropin-sensitive cholin ester, indistinguishable from those of acetylcholine, so far as they can be tested in the venous blood collected during vagus stimulation "

Under certain conditions, parasympathomimetic substance may be found in the venous blood For example, Feldberg and Rosenfeld (1933) found an acetylcholine-like substance in the portal blood following the intravenous administration of physostigmin, but none could be detected in other vessels, *e g*, the jugular and femoral veins On the basis of their findings, they concluded that acetylcholine is constantly produced in the gastro-intestinal wall, and, under normal conditions it is rapidly converted into choline When its conversion is prevented by physostigmin, the acetylcholine flows out in the portal vein Unlike sympathin, therefore parasympathin, under normal conditions probably is not transported to distant organs through the circulating blood Evidence bearing on this point which seems to be conclusive is afforded by the results of experiments reported by Freeman, Phillips and Cannon (1931) Using the completely denervated iris and submaxillary gland, the blood pressure, the denervated heart (with intrinsic parasympathetic neurons present) and the denervated tongue as indicators, they tested the effect of stimulating the entire vagus distribution below the cardiac branches Although a bypass for the blood

from the portal vein to the inferior vena cava was arranged in order to avoid possible destruction of the substance in question by the liver, and although in some of the experiments anesthetics were avoided, only negative results were obtained. It must be assumed, therefore, that the effect of the parasympathetic substance *is quite local*. *This assumption also is in* accord with the view that the parasympathetic nerves, as a rule, distribute directly to the tissues innervated. They appear to be organized for relatively localized action rather than for such diffuse effects as are produced by sympathetic stimulation augmented by the influence of adrenin and sympathin.

Certain organs whose efferent innervation is effected solely through sympathetic nerve components have long been known to react to certain chemical agents as would be expected if they were innervated through parasympathetic nerves. The chemical mediator liberated as a result of stimulation of such sympathetic nerves also possesses the properties of parasympathin. Stimulation of certain parasympathetic nerves also results in the liberation of a chemical substance probably identical with sympathin (Dale, 1938). These facts seemed to call for a new classification of autonomic nerve fibers according to their chemical function, as distinct from their anatomical connections. Accordingly, Dale proposed that nerve fibers whose stimulation results in liberation of sympathin or an adrenin-like mediator be referred to as adrenergic and those whose stimulation results in liberation of parasympathin, or an acetylcholine-like mediator, as cholinergic. The almost universal adoption of these terms may be regarded as evidence of their appropriateness and the need which they have met. In view of the role of the chemical mediators in the transmission of nerve impulses and the finding that adrenergic neurons contain adrenin but not acetylcholine, whereas cholinergic neurons contain acetylcholine but not adrenin (Cannon and Lissák, 1939), the classification of autonomic nerve fibers in adrenergic and cholingeric categories is more significant than their classification according to sympathetic or parasympathetic origin.

Data reported by Luco and Lissák (1938) support the assumption that activation of sympathetic fibers following degeneration of the corresponding preganglionic axons results in liberation of adrenin-like substance in greater concentration than activation of the corresponding fibers on the normally innervated side. Goffart (1939) and Goffart and Bacq (1939) also reported an increased concentration of acetylcholine in the gastrointestinal tract following degeneration of the divided vagus nerves.

The chemical mediator liberated in the autonomic ganglia when the preganglionic fibers are stimulated resembles acetylcholine. According to Feldberg and Gaddum (1933), it probably is identical with the latter substance. In order to test this hypothesis, they perfused the superior cervical sympathetic ganglia in cats with salt solutions and applied various pharmacological tests to the outflowing liquid. In the absence of physostigmin no activity was detected but, when physostigmin was added to the perfusion liquid in order to inhibit the destruction of acetylcholine, the liquid collected exhibited the properties of a solution of the later substance. The theory that the substance in question possesses the biological properties of acetylcholine is now abundantly supported by data reported by various investigators.

Although the liberation of an acetylcholine-like substance in the autonomic ganglia resulting from stimulation of the preganglionic fibers is conceded, there is no general agreement regarding the mechanism of the transmission of impulses from preganglionic axons to ganglion cells This problem has engaged the attention of not a few investigators The available data have been interpreted by some as supporting the theory of humoral transmission and by others as supporting the theory of electrical transmission The former regard the presynaptic action potential as a factor which is operative mainly or exclusively in the liberation of the acetylcholine-like mediator in the ganglion The latter support the assumption that transmission of the impulse across the synapse is effected in essentially the same manner as its propagation along the preganglionic axon According to this assumption the humoral substance present in the ganglion serves mainly to counteract fatigue and exerts a local vasodilator influence while the nerve impulse is transmitted by the presynaptic action potential The humoral substance liberated in the autonomic ganglia has also been regarded as a non specific metabolic product (Lorente de Nó, 1938) and as a regulator of nerve transmission (Schaefer and Haas, 1939) Certain investigators particularly Coppée and Bacq (1938), Lanari and Rosenblueth (1939), Cannon (1939) and Feldberg (1943) have been led to conclude that an acetylcholine-like mediator is indispensable for transmission through a ganglion Coppée and Bacq do not regard this conclusion as implying that the theory of electrical transmission must be discarded Certain data advanced by Lanari and Rosenblueth seem to support the assumption that transmission at the synapses in the autonomic ganglia is accomplished by a process which is essentially similar to that of transmission at the neuro-effector junctions Failure of transmission at the synapses during the early stages of Wallerian degeneration of the preganglionic axons and during fatigue probably is due to liberation of the acetylcholine-like substance in the ganglion in insufficient concentration (Cannon, 1939) In experiments reported by Feldberg (1943) the distal portion of the cervical sympathetic trunk lost its capacity to synthesize acetylcholine in an early stage of degeneration following section below the superior cervical sympathetic ganglion This loss preceded failure of conduction In the superior cervical ganglion it coincided with the time interval during which synaptic transmission became impaired These results seem to warrant the conclusions that synthesis of acetylcholine is a property of the terminal portions of preganglionic fibers and that the production of acetylcholine is an essential preliminary for normal and particularly sustained synaptic transmission The electrical phenomena associated with transmission at the synapse cannot be disregarded, but until the protagonists of the electrical theory can display an instance of transmission through an autonomic ganglion without acetylcholine, their theory cannot be regarded as on the same footing as that of chemical transmission

Sensitization of Denervated Tissues to Chemical Mediators —Structures which have lost their proper nervous connections become increasingly sensitive to chemical stimuli This phenomenon has been studied extensively by Cannon and his collaborators On the basis of their results and those of other workers Cannon formulated the law of denervation as follows "When in a series of efferent neurons a unit is destroyed, an

increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated "

This law is well illustrated in the sensitivity changes which take place in smooth muscles and glands following section of either the postganglionic or the preganglionic sympathetic fibers For example, if the sympathetic innervation of the iris is interrupted, the pupil, under certain conditions following degeneration of the sympathetic fibers, is more widely dilated than the one of the normally innervated eye on the opposite side This paradoxical reaction was explained by Meltzer and Auer (1904) who observed, in rabbits and cats, that one or two days after removal of the superior cervical ganglion a selected dose of adrenin caused marked dilatation of the pupil and constriction of the blood vessels of the ear on the operated side but had no effect on the other side Cannon and Hoskins (1911) and Cannon and de la Paz (1911) showed that this reaction, elicited by emotional excitation, is due to the discharge of adrenin into the blood stream This finding was further corroborated by Elliott s (1912) observation that the paradoxical reaction of the sympathetically denervated iris disappears following extirpation of the adrenal glands

In experiments reported by Hampel (1935), the smooth muscle of the nictitating membrane became increasingly sensitive to graded doses of adrenin for about a week following extirpation of the superior cervical ganglion, and then more slowly until a maximum state of sensitivity was reached at the end of 14 to 16 days, which may continue for many months If the nerve supply to a sympathetically denervated nictitating membrane regenerates the increased sensitivity of its muscle to adrenin gradually subsides to its previous level (Simeone, 1937)

Sensitization of the vascular musculature in a sympathectomized extremity to adrenin in the circulating blood has been reported by various investigators In cases of Raynaud's disease, for example sympathetic denervation by means of ganglionectomy may abolish vascular spasm but the vascular musculature becomes exquisitely sensitive to circulating adrenin (Freeman Smithwick and White, 1934) Such sensitization is less marked if paralysis of the vasomotor nerves is effected by section of the preganglionic fibers, leaving the ganglion cells with their axons intact (White 1935) Data reported by Simmons and Sheehan (1939) seem to indicate that the increased sensitivity of the vascular musculature following sympathectomy reaches its maximum in 8 to 10 days and then gradually subsides and may disappear completely

Smooth muscle which is normally inhibited by sympathetic stimulation undergoes a corresponding change in sensitivity to adrenin following interruption of its sympathetic innervation For example a portion of the intestine long deprived of its sympathetic nerves is more persistently inhibited by adrenin than a freshly denervated portion (Luco 1937 Youmans 1938) The musculature of the sympathectomized non-pregnant cat's uterus reacts in a similar manner

Interruption of the parasympathetic innervation of smooth muscle likewise is followed by increased sensitivity of the muscle to parasympathomimetic substances Increased responsiveness of the pupilloconstrictor muscle to pilocarpine following extirpation of the ciliary ganglion was demonstrated by Anderson (1905) Shen and Cannon (1936) demonstrated a similar reaction of the parasympathetically denervated pupil-

loconstrictor muscle to acetylcholine Smooth muscle innervated by cholinergic sympathetic fibers likewise becomes hypersensitive to acetylcholine following degeneration of these fibers

Glands also exhibit increased responsiveness to chemical stimuli following denervation Maes (1938) reported that extirpation of the superior cervical sympathetic ganglion caused no immediate change in the responsiveness of the lacrimal gland to intravenous injections of adrenin, pilocarpine or acetylcholine but when the tests were made eleven days or more after the operation the drugs caused greater secretory activity of the denervated gland than of the one on the control side Simeone and Maes (1939) reported increased responsiveness of the submaxillary gland in cats to intravenous injections of adrenin acetylcholine and pilocarpine forty-seven to ninety days after extirpation of the superior cervical ganglion The increased responsiveness was greatest to pilocarpine and least to acetylcholine Pierce and Gregersen (1937) observed increased responsiveness of the submaxillary gland to intravenous injections of pilocarpine following its parasympathetic denervation by section of the chorda tympani This effect could be recognized within six days after the operation It was fully developed within two or three weeks and continued undiminished for six months or longer

The data cited above indicate that both smooth muscle and glands following denervation become more responsive not only to chemical agents which are their natural stimulants but also to certain other agents After deprivation of its adrenergic fibers the nictitating membrane, according to Rosenblueth (1932), becomes hyperresponsive not only to adrenin but also to acetylcholine, pilocarpine and eserine The lacrimal and submaxillary glands, denervated either by ganglionectomy or section of the preganglionic fibers, also exhibit a lack of specificity with regard to the stimulating agents which elicit secretory hyperactivity

Since the transmission of impulses at the synaptic contacts of the preganglionic fibers with the autonomic ganglion cells involves an acetylcholine-like mediator, it seems reasonable to assume that interruption of the preganglionic fibers might result in hyperresponsiveness of the ganglion cells to acetylcholine In a series of carefully controlled experiments, Cannon and Rosenblueth (1936) obtained certain data which support this assumption It is further supported by data reported by Simeone, Cannon and Rosenblueth (1938) and Simeone and Maes (1939)

The mechanism of sensitization of denervated effector organs to adrenin or acetylcholine is not fully understood The most plausible explanation which has been advanced is based on the assumption that the permeability of the surface membranes of the effector cells is increased following interruption of their nerve supply This point of view is supported by the fact that the increased sensitivity is not absolutely specific for adrenin and acetylcholine but exists in some degree also to other stimulating agents For example the denervated nictitating membrane is sensitized not only to adrenin but also to acetylcholine pilocarpine, histamine and potassium ions It is further supported by the fact that the electrical potential accompanying the contraction of smooth muscle is decreased following denervation, probably due to diminished polarization of the cell membranes resulting from increased cell permeability

Action of Drugs in Relation to the Sympathetic and the Parasympathetic Nerves.—Studies involving the action of various pharmacologic agents on the organs innervated through the autonomic nervous system have contributed greatly to our knowledge of the functional relationships of the autonomic nerves. Certain poisons, *e. g.*, nicotine, affect both the sympathetic and parasympathetic nerves in essentially the same manner. Other pharmacologic agents exert a specific action on tissues innervated by either adrenergic or cholinergic autonomic fibers but do not influence both adrenergic and cholinergic functions. Adrenin and certain other substances produce effects which, with certain exceptions, are similar to the effects produced by stimulating adrenergic nerves. Pilocarpine, muscarine, physostigmine and choline produce effects which, in most cases, are similar to the effects produced by stimulating cholinergic nerves. Ergotoxine and ergotamine first stimulate adrenergic nerves, then block conduction to the effector organs innervated by them. Atropine exerts the same effect on effector organs innervated through cholinergic nerves. These facts indicate a fundamental chemical difference between adrenergic and cholinergic neurons. They also have an important bearing on the action of hormones on the tissues.

The essential functional relationship between the preganglionic and ganglionic neurons was discovered by the use of nicotine. Langley first observed that when a nicotine solution is applied to an autonomic ganglion, regardless of whether it belongs to the sympathetic or the parasympathetic division of the autonomic system, stimulation of the preganglionic fibers is no longer effective, although stimulation of the postganglionic fibers still elicits the characteristic response. Similar results also were obtained when a weak solution of nicotine was injected into the blood stream. He, therefore, concluded that nicotine acts on the synaptic connections of the preganglionic axons with the ganglionic neurons to prevent conduction through these neuron junctions. Bayliss and Starling (1899) observed the same effect of small doses of nicotine on the visceral efferent chains supplying the gastro-intestinal musculature. This result led them to conclude that all effects of the vagus on the enteric musculature are completely abolished by minimal doses of nicotine (0.3 cc. of a 1 per cent solution). This observation has been corroborated by not a few later investigators. When nicotine is administered in gradually increasing doses, stimulation of the vagus nerves again becomes effective when 25 to 50 mgm. per kilo of body weight has been administered (Thomas and Kuntz, 1926). In our experiments, still larger doses of nicotine (50 to 500 mgm. per kilo) further augmented the responses of the intestinal muscle to vagus stimulation so that the amplitude of the contractions in response to the same stimulus became greater than before nicotine was administered. Massive doses of nicotine (2000 mgm. or over per kilo) finally caused paralysis of the intestinal vagi from which they did not recover during the period of observation. These findings have been corroborated by the work of Mulinos (1927) on the cat.

Classification of Autonomic Drugs.—Pharmacologic agents which influence autonomic functions act upon the tissues innervated by the autonomic nerves either to stimulate or depress the functions of the effector cells. In the older classifications these agents were grouped as sympathetic stimulants and depressants and parasympathetic stimulants and depressants.

Such classifications obviously do not take into consideration the chemical characteristics of the neurons in question or the sites of action of the drugs. The older concept of stimulation and depression of the nerve terminals by pharmacologic agents is untenable in the light of the demonstration of their effects on completely denervated effector organs (Enderlen and Eismayer, 1927) and embryonic structures in which nerves have not yet made connections with the effector cells. Since the so-called autonomic drugs stimulate or depress not the nerve endings but the effector cells, it is more advantageous to classify them in categories which indicate their relationships to one another and to their sites of action. Consequently, they may be classified as drugs which act upon cells innervated by (1) preganglionic cholinergic nerves, (2) postganglionic cholinergic nerves, and (3) adrenergic nerves. A partial list of these substances is given in the following table:

	Drugs acting on cells innervated by preganglionic cholinergic nerves	Drugs acting on cells innervated by postganglionic cholinergic nerves	Drugs acting on cells innervated by adrenergic nerves
Stimulants	Acetylcholine Acetyl beta methylcholine Carbaminocholine Physostigmine Prostigmine	Acetylcholine Acetyl beta methylcholine Physostigmine Prostigmine Pilocarpine Muscarine Arecoline	Adrenin Ephedrine Benzedrine
Depressants	Nicotine	Atropine Scopolamine Hyoscyamine Homatropine	Ergotoxine Ergotamine

Since adrenin and acetylcholine are representative of the chemical mediators liberated in relation to the effector cells when impulses reach the terminal structures of adrenergic and cholinergic nerve fibers respectively, it cannot be regarded as appropriate to designate them as sympathomimetic and parasympathomimetic. On the other hand it may be convenient, at least for descriptive purposes, to refer to the other autonomic drugs in this manner, keeping in mind of course that the sympathomimetic substances act upon all effector cells innervated by adrenergic nerves and the parasympathomimetic substances, on all effector cells innervated by cholinergic nerves.

Autonomic Drug Action.—The sequence of events by which nerve impulses elicit responses in effector cells may be outlined schematically as follows:

1. Propagation of impulse in preganglionic neuron.
2. Liberation of chemical mediator (acetylcholine) at neuro-neural junction.
3. Propagation of impulse in ganglionic neuron.
4. Liberation of chemical mediator (sympathin or parasympathin) at neuro-effector junction.
5. Action of mediator on effector cell.
6. Specific effector response.

The relation of acetylcholine to the mediation of nerve impulses at neuro-effector junctions and in the autonomic ganglia has already been discussed. When introduced into the body, this substance acts directly

on cholinergic autonomic effector organs, ganglion cells and skeletal muscle. The similarity of the action of acetylcholine to that of muscarine on autonomic effector organs (smooth muscles and glands) has given rise to the term "muscarine" actions of acetylcholine to distinguish them from its effects on ganglion cells. Like nicotine, acetylcholine in low concentrations exerts a stimulating effect on ganglion cells and skeletal muscles and in high concentrations depresses them. Its stimulating action on ganglion cells and skeletal muscles, therefore, has been termed "nicotinic." These actions of acetylcholine contrast not only in regard to the effector organs involved but also in respect to the drugs which block them. For example, nicotine blocks the nicotinic action of acetylcholine, particularly in the ganglia, whereas atropine blocks only its muscarinic actions.

Other esters of choline, such as acetyl beta methylcholine and carbaminoylcholine presumably act in a manner similar to that of acetylcholine but exhibit greater selectivity for particular effector cells. Their nicotinic actions are less marked than those of acetylcholine but they possess greater muscarinic potency. Pilocarpine, muscarine and arecoline are highly selective for structures innervated by cholinergic postganglionic nerves. Their actions simulate the muscarinic actions of acetylcholine but not the nicotinic. They do not inhibit cholinesterase as does physostigmine, and elicit responses in smooth muscle and glands after complete nerve degeneration.

Physostigmine (eserine) and prostigmine do not act directly on effector cells but produce responses in effector organs by temporarily inhibiting the destructive effect of cholinesterase on the acetylcholine liberated at the neuro-effector junctions by impulses conducted through cholinergic fibers. Their sites of action consequently, are the same as those of acetylcholine.

The relation of adrenin to the chemical mediation of adrenergic nerve impulses has already been discussed. When introduced into the body, this substance acts directly on smooth muscle and gland cells. Sympathomimetic drugs such as ephedrine and benzedrine are closely related to adrenin chemically and also act directly on cells innervated by adrenergic nerves. They differ from adrenin mainly in that their excitatory actions are not reversed by ergotoxine and their effects are not potentiated by cocaine.

Atropine exerts no effect on the nicotinic actions of acetylcholine but blocks the muscarinic actions of this substance regardless of whether the latter are excitatory, as in the intestine, or inhibitory, as in the heart. It is less effective in blocking certain other effects of nerve stimulation. A complete explanation of the actions of atropine in blocking the effects of certain cholinergic nerve impulses and not those of others cannot be offered on the basis of our present knowledge. It seems probable that in blocking the effects of nerve stimulation atropine does not prevent the release of acetylcholine at cholinergic nerve endings but prevents the acetylcholine released from entering the effector cells.

Ergotoxine and ergotamine block only the excitatory effects of adrenin or stimulation of adrenergic nerves. They neither prevent the release of the chemical mediator at adrenergic nerve endings nor interfere with its union with the receptive substance, but probably block the contractile or secretory mechanisms in the effector cells directly.

The predominant effect of most autonomic drugs is exerted peripherally. Certain drugs, *e g*, amidopyrine and ether, exert a direct influence on the central autonomic centers. The influence of amidopyrine on blood sugar obviously is exerted through centers in the brain stem, since it is abolished by the administration of brain stem narcotics (Hogler, 1932). In experiments reported by Bhatia and Burn (1933), the stimulating effect of ether on the sympathetic nerves was abolished by pithing the animals (cats), whereas, in decerebrate cats with the adrenals removed, ether caused contraction of the spleen, inhibition of the intestine and the virgin uterus and acceleration of the cardiac rhythm.

Recognition of the action of pharmacologic agents on central autonomic mechanisms is beset with certain difficulties. In order to demonstrate central action, according to Haas (1938), the drug must be introduced into the central nervous system through the cerebrospinal fluid. If, when administered in this manner, doses too small to affect peripheral autonomic structures through the blood produce autonomic reactions the substance must act on autonomic centers. If the dose required to elicit an autonomic response is large enough to produce a peripheral reaction through the blood, central action is precluded. The results of experiments reported by Haas indicate definite central action of picrotoxin and strongly suggest that adrenin and pilocarpine may exert a direct action on central autonomic centers. Central action of acetylcholine and ergotamine was not apparent in his experiments except when the dosage administered was large enough to cause marked poisoning, with central nervous reactions which could not be differentiated from the peripheral reactions.

Homeostasis — The living tissues of the body are not directly exposed to the external environment but exist in a liquid matrix, the internal environment, which normally is maintained in a more or less constant state. The constancy of the internal environment, or homeostasis, depends mainly on the functional integrity of the sympathetic division of the autonomic nervous system (Cannon 1930). Elimination of the sympathetic nerves is not incompatible with life under favorable conditions but results in certain functional defects which are more marked in some species than in others. Animals have been kept alive and apparently in good health for many months following complete surgical removal of both sympathetic trunks (Cannon *et al*, 1927, 1929). The functional defects resulting from complete sympathetic denervation are apparent particularly in the decreased capacity of the animals to withstand high and low external temperatures, lowering of the basal metabolic rate, diminished resistance to anoxemia, increased sensitivity to injected insulin and diminished capacity for compensatory reactions to successive hemorrhages.

In an extensive study of homeostasis in cats reported by Sawyer *et al* (1933), animals which had been subjected to complete extirpation of both sympathetic trunks, when placed in a superheated room (40° C), exhibited a greater rise in body temperature than normal animals. In a cold room their body temperature dropped markedly, whereas normal animals in the same environment usually responded with a slight rise in body temperature. In atmosphere in which the oxygen tension was reduced to 6 to 8 per cent, the sympathectomized animals fainted within fifteen to thirty-seven minutes, whereas the normal animals did not collapse for at least one hour. Both sympathectomized and normal animals responded to

large doses of insulin (0 5 unit per kg) with a rapid decrease in blood sugar to nearly the level at which the symptoms of hypoglycemia appear The normal animals then begin to show an increase in blood sugar and spontaneous recovery, whereas the sympathectomized ones underwent further decrease in blood sugar until the convulsive stage was reached and spontaneous recovery did not take place Sympathectomized animals showed only a slight compensatory reaction or none at all to a single removal of 13 to 15 per cent of the total blood volume whereas normal ones withstood three or four bleedings of equal intensity before the compensatory vasoconstrictor reaction failed to raise the blood pressure

In experiments reported by Hodes (1939), completely sympathectomized cats were able to run much less rapidly and for markedly shorter periods without becoming fatigued than before operation Their cardiac acceleration after exercise was 30 per cent less than that of normal cats, but greater than that caused by removal of vagus inhibition This probably is attributable to the effect of accelerator fibers in the vagus nerves The capacity of the sympathectomized cats for muscular exercise was increased by administration of adrenin

The effects of complete sympathectomy are less marked in dogs than in cats Completely sympathectomized dogs are not abnormally sensitive to heat and cold (Bacq *et al* , 1934) Neither is their capacity for vigorous muscular exercise materially reduced (Brouha Cannon and Dill, 1936) In an intensive study in which dogs which had been subjected to complete extirpation of the sympathetic trunks were compared with normal dogs with respect to their reactions to heat and cold, anoxemia and insulin hypoglycemia, McDonough (1939) found no significant difference in the maximum decrease in body temperature in the two groups when subjected to low environmental temperature and no noteworthy difference in the rise in body temperature or the rate of panting when subjected to high environmental temperatures In cold environments shivering began earlier and continued at a faster rate in the sympathectomized dogs than in the normal ones The sympathectomized dogs seemed to be able to endure an oxygen tension of 6 per cent for five hours as well as the normal ones In an atmosphere in which the oxygen tension was reduced to 4 per cent respiratory failure occurred in both groups of animals, but earlier in the sympathectomized than in the normal ones The former showed hypersensitivity to injected insulin by a greater decrease in the percentage of blood sugar and more frequent occurrence and greater severity of the symptoms of hypoglycemia than the latter which received the same insulin dosage The fasting blood sugar level was the same in both groups of animals

The remarkable capacity of completely sympathectomized dogs, as compared with completely sympathectomized cats, to endure unfavorable environmental conditions is attributed to various accessory physiological mechanisms, not controlled by the sympathetic nerves, which the dog possesses as a running animal Among these may be mentioned larger lungs and heart per kilogram of body weight, greater blood volume, higher hemoglobin content abundant production of saliva and a tongue with a large surface area for elimination of heat These mechanisms are of no avail in insulin hypoglycemia, with respect to which dogs and cats react in essentially the same manner

In a series of experiments carried out to determine the influence of heat and cold on the vago insulin and the sympathetico-adrenal systems, Gellhorn, Cortell and Feldman (1941) exposed (A) normal, (B) adrenodemedullated, (C) vagotomized and (D) adrenodemedullated-vagotomized rats to cold by immersing them in water at 2° to 4° C for ten minutes, and to heat by placing them in an environmental temperature of 32° to 36° C for six hours The animals in group A reacted to cold with hyperglycemia, those in group B, with hypoglycemia, those in group D, showed no significant change in blood sugar On exposure to heat the animals in group A reacted with delayed hypoglycemia, those in group B with hypoglycemia during the entire period those in group C with hyperglycemia and those in group D showed no significant change in blood sugar The results of these experiments support the assumptions that both the vago-insulin and the sympathetico adrenal systems react to cold but the latter more strongly than the former, and that both systems also react to heat but the former more strongly than the latter The results of previous investigations (Feldman, Cortell and Gellhorn, 1940) have demonstrated that both the vago-insulin and sympathetico-adrenal systems react to anoxemia, emotional excitement, certain drugs such as metrazol and cocaine, and electrically induced convulsions Of all the procedures thus far applied, subjecting the animals to heat is the only one which has resulted in stronger stimulation of the vago-insulin system than of the sympathetico-adrenal, as indicated by the change in blood sugar The predominance of the reaction of the vago insulin system on exposure to high environmental temperature probably tends to counteract the harmful effects of overheating just as the predominance of the reaction of the sympathetico-adrenal system tends to counteract the deleterious effects of cooling not only by increasing heat production but also by bringing about vasoconstriction

Total and subtotal extirpation of the sympathetic trunks in man have been reported by Grimson, Alving and Adams (1941), who carried out the operations on patients with high blood pressure These operations, carried out in several stages, according to their account, are not incompatible with a relatively normal existance Following operation the patients showed postural hypotension and decreased heart rate, but no marked changes in gastro-intestinal, urinary and respiratory functions The capacity for adjustment to changes in environmental temperature obviously is decreased since the denervated sweat glands are no longer functional and the cutaneous vessels do not respond reflexly to thermal stimulation

The regulation of body temperature which, in the intact animal, is mediated through the autonomic nerves is controlled mainly through autonomic centers in the brain stem Spinal animals, *i e*, animals in which the spinal cord is transected or otherwise interrupted in the cervical region, are unable to make the adjustments necessary to maintain normal body temperature The data bearing on this problem are somewhat conflicting but those reported by the majority of the more recent investigators indicate serious loss of the capacity to regulate against either high or low environmental temperatures following transection of the spinal cord in the cervical region In an extensive series of experiments reported by Issekutz *et al* (1937), cats with the spinal cord transected in the cervical region were able to maintain normal body temperature only when the environmental temperature was kept at approximately 80° F Somewhat similar

results have been reported by Herman *et al* (1938, 1939) The results of experiments reported by Clark (1940) indicate that cervical spinal cats are incapable of maintaining normal body temperature when subjected to a sudden marked decrease in environmental temperature but are capable of a limited slow adjustment to cold if the environmental temperature is lowered gradually The increased ability to withstand low external temperature which is acquired in this manner is lost after the animals have again been kept in a warmer environment The ability of cervical spinal animals to maintain normal body temperatures when subjected to changes in environmental temperature which occur very gradually and within the narrow range ordinarily regarded as comfortable depends on a supplementary slow adjustment which probably is hormonal in nature (Ranson, 1940)

The chief centers involved in the regulation of body temperature are located in the hypothalamus This function of the hypothalamus is discussed at length in another connection (see p 86)

CHAPTER VI

DEVELOPMENT

Historical Survey.—The autonomic ganglia and nerves are related developmentally to the cerebrospinal nervous system. Their primordia arise relatively early in embryonic development and are composed of cells which are displaced from the neural tube and cerebrospinal ganglia. The majority of the early investigators, including Balfour (1877), Schenck and Birdsall (1878), Onodi (1886), His, Sr. (1890), His, Jr. (1891), Marshall (1893), Hoffmann (1900, 1902), and Kohn (1905, 1907), supported the theory that the cells which make up the primordia of the ganglia of the sympathetic trunks and prevertebral plexuses are derived exclusively from the spinal ganglia or neural crests. The development of the autonomic plexuses more intimately associated with the thoracic and abdominal viscera, *e. g.*, the cardiac, pulmonary and enteric plexuses, was not studied intensively by these early investigators but it was assumed quite generally that the nerve cells in all the autonomic ganglia except those in the head are derived from the same cerebrospinal sources.

Froriep (1907) traced cells of medullary origin into the primordia of the sympathetic trunks via the ventral nerve roots and communicating rami and advanced the opinion that the sympathetic ganglion cells are derived mainly from the neural tube. Cajal (1908) concurred in this opinion on the basis of his findings.

The early data bearing on the development of the autonomic ganglia in the head, except the ciliary ganglion, are fragmentary. Hoffmann (1885), Ewart (1890) and Chiarugi (1894) supported the theory that the primordium of the ciliary ganglion is made up of cells which are displaced from the semilunar ganglion either directly or via the ophthalmic nerve. Beraneck (1884), Reuter (1897), and Rex (1900) described the primordium of this ganglion as arising in connection with the oculomotor nerve but they did not determine the sources of its cells. Carpenter (1906) described the early primordium of the ciliary ganglion in the chick as composed of cells which are displaced from the mid-brain via the oculomotor nerve. According to his account, this primordium later receives cells also from the semilunar ganglion via the ophthalmic nerve. In the absence of adequate data bearing on the development of the other autonomic ganglia in the head, it was quite generally assumed that the sphenopalatine, otic and submaxillary ganglia arise from primordia composed exclusively of cells derived from the semilunar ganglion.

Such, in brief, was the status of our knowledge of the development of the autonomic nervous system when the present writer initiated a series of studies on the development of this system and its histogenetic relationship to the cerebrospinal nervous system. The results of the earlier studies in this series (1909–1914) showed clearly that the autonomic ganglia bear the same histogenetic relationship to the cerebrospinal nervous system in all classes of vertebrates although they may differ somewhat in their morphogenesis in the several classes. The observations of Froriep and Cajal regarding a contribution of cells of medullary origin to the

primordia of the sympathetic trunks via the ventral spinal nerve roots were corroborated Cells were also traced from these primordia into the primordia of the prevertebral plexuses, but not into the plexuses which are functionally related to the vagi viz the cardiac, pulmonary and enteric plexuses On the contrary, the cells composing the primordia of the latter plexuses were traced distalward along the vagi and their branches This finding was corroborated by Abel (1912) in embryos of the chick, and by Stewart (1920) in embryos of the rat The primordia of the autonomic ganglia in the head according to the writer's (1920) observations, include both cells which are displaced distalward along the nerves which convey the preganglionic fibers to the several ganglia respectively and cells which advance peripheralward along the respective divisions of the trigeminal nerve

Among the more recent investigators whose findings support the theory that the primordia of the sympathetic trunk ganglia are composed at least in part of cells derived from the neural tube via the ventral spinal nerve roots may be mentioned Gaufini (1911–1918), Hau and Johnson (1923) Uchida (1927), Haven (1937) and Jones (1937–1943) Uchida, whose observations were based on embryos of reptiles (Trigonocephalus), birds (chick) and mammals (cat dog mouse pig calf), also concluded on the basis of his findings, that the enteric plexuses in the esophagus and stomach and the cardiac and pulmonary plexuses comprise mainly cells which are displaced distalward along the vagi but the primordia of the enteric plexuses in the intestine early comprise only cells of sympathetic origin and later receive cells of vagus origin On the basis of extensive experimental studies carried out on chick embryos Jones supports the assumptions that only cells of medullary origin become differentiated into autonomic ganglion cells and that those which become sympathetic and parasympathetic ganglion cells respectively are displaced distalward along the efferent roots of the nerves which convey the corresponding preganglionic outflows

Contrary to nearly all the more recent investigators in this field F Muller (1920), Muller and Ingvar (1923) and Van Campenhout (1929, 1930) opposed the theory that cells of medullary origin are displaced into the sympathetic primordia and supported the older theory that the primordia of the sympathetic trunks comprise only cells which are derived from the spinal ganglia or neural crests On the basis of further experimental studies Van Campenhout (1932) conceded that the ganglia of the cardiac and pulmonary plexuses comprise cells of vagus origin but maintained that those of the enteric plexuses throughout the intestine comprise only cells of sympathetic origin

Embryological Data[1]**—Sympathetic Trunks**—The primordia of the ganglia of the sympathetic trunks appear earliest in the lower thoracic and upper abdominal regions They are composed of aggregates of cells of nervous origin lying along the dorsolateral aspects of the aorta (Fig 27) These cells are somewhat scattered and may be differentiated from the cells of the mesenchyme by the somewhat larger size and more intense staining

[1] The following descriptive account of the development of the autonomic nervous system is based mainly on an investigation carried out by the writer (1920) on preparations of human embryos included in the Carnegie Embryological Collection made available through the courtesy of Dr G L Streeter Director of the Department of Embryology Carnegie Institution of Washington

reaction of the nucleus (Fig 28) Such aggregates of cells may be observed from the lower cervical to the sacral region in human embryos 6 mm in length They are arranged segmentally but, by reason of the marked curvature of the embryo, they lie so close together that they constitute a continuous column of loosely aggregated cells This condition obtains until the embryos have attained a length of 9 to 10 mm , when the sympathetic primordia are present from the upper cervical to the sacral region The segmental character of the sympathetic primordia gradually becomes apparent, as development advances, and the cell aggregates become connected by longitudinal fibers In the cervical and upper thoracic segments the sympathetic primordia lie along the dorsolateral aspects of the descending aortae and in close proximity to the latter The position of these primordia seems to be determined, at least in part, by the position of the paired descending aortae Inasmuch as these vessels lie at an appreciable

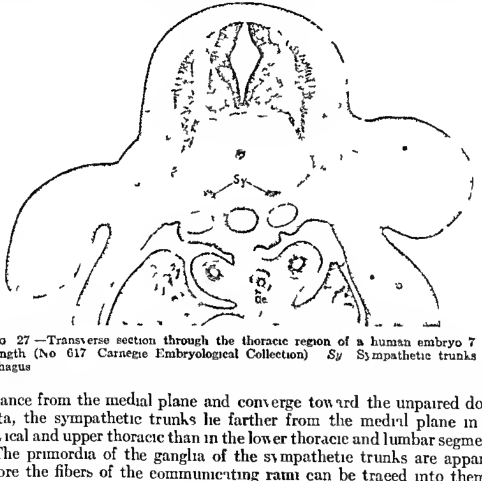


FIG 27 —Transverse section through the thoracic region of a human embryo 7 mm in length (No 617 Carnegie Embryological Collection) *Sy* Sympathetic trunks *Oe* esophagus

distance from the medial plane and converge toward the unpaired dorsal aorta, the sympathetic trunks lie farther from the medial plane in the cervical and upper thoracic than in the lower thoracic and lumbar segments

The primordia of the ganglia of the sympathetic trunks are apparent before the fibers of the communicating rami can be traced into them in material prepared by the ordinary methods In preparations of human embryos 7 mm and over in length, the fibers of the communicating rami extend into the sympathetic primordia throughout the greater part of the thorax and abdomen (Fig 28) In preparations of embryos which are somewhat farther advanced fibers tend ventralward from the primordia of the sympathetic trunks and enter the primordia of the ganglia of the prevertebral plexuses, which are represented by scattered aggregates of cells along the ventrolateral aspects of the abdominal aorta (Fig 29) These primordia arise by the ventral displacement of cells from the primordia of the sympathetic trunks

The majority of the cells in the sympathetic primordia in early embryos are identical in appearance with the cells in the spinal ganglia and the indifferent cells in the mantle layer in the neural tube. *Cells of the same* character are present in the paths of the dorsal and ventral nerve roots

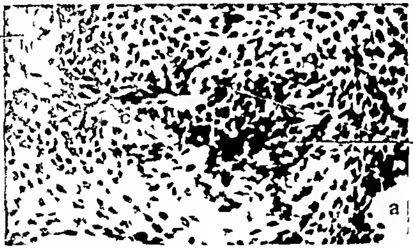


Fig. 28 —Transverse section through lower thoracic region of a human embryo 7 mm in length showing spinal nerve and sympathetic trunk. *a* Aorta, *C* communicating ramus, *SP* spinal nerve, *Sy* sympathetic trunk

and communicating rami. Occasionally an individual cell, the nucleus of which lies partly within and partly without the external limiting membrane may be observed in a ventral nerve root. Cells in this position obviously are in the process of emerging from the neural tube. Likewise cells become

Fig. 29 —Transverse section through the abdominal region of a human embryo 10.1 mm in length showing primordia of sympathetic trunks and prevertebral plexuses. *a* Aorta, *PV* prevertebral plexuses, *Sy* sympathetic trunks

separated from the distal ends of the spinal ganglia and advance along the dorsal nerve root. Since the cells of medullary and spinal ganglion origin appear identical in early embryos, it is impossible to distinguish between the cells derived from these two sources distal to the junction of the dorsal

and ventral nerve roots The evidence at hand favors the assumption that cells from both these sources enter the sympathetic primordia

According to the writer's observations on human and other vertebrate embryos, cells of cerebrospinal origin are present in the sympathetic primordia before fibers of the communicating rami can be traced into these locations in material prepared by the ordinary methods Certain other investigators have also expressed the opinion that many of the cells which enter the sympathetic primordia migrate peripheralward in advance of the growing nerve fibers Streeter (1912) observed cells which enter the primordia of the ganglia of the sympathetic trunks advance toward the aorta before fibers are present in the communicating rami, consequently, he described the communicating rami in early human embryos as cellular strands Ganfini (1917) described the communicating rami in early mammalian embryos (guinea pig, pig) in the same manner Since it is known that the distal portions of growing nerve fibers are not brought out clearly by the ordinary processes of staining, it may be assumed that fibers of the communicating rami extend well into the sympathetic primordia somewhat earlier than the recorded data seem to indicate, but the earliest cells probably enter the primordia of the sympathetic trunks somewhat in advance of the growing nerve fibers

In preparations of human embryos 9 to 10 mm in length, cells of cerebrospinal origin are still abundant in the spinal nerve trunks and communicating rami, indicating that the peripheral displacement of these cells is still going on It probably does not continue much beyond the stage of embryos 11 or 12 mm in length The cells in the sympathetic primordia also are more numerous and are arranged more compactly than in the earlier embryos Mitotic figures in the sympathetic primordia also indicate that the cells increase in number by local proliferation

The primordia of the sympathetic trunks arise somewhat later in the cervical region than in the thoracic This fact was noted by all the earlier investigators who made special mention of the development of the cervical portion of the sympathetic trunks in the embryos of the higher vertebrates Some of them also observed that these primordia gradually extend cephalad from the upper thoracic level as continuous columns of cells until they reach the upper cervical segments According to Ganfini (1917), cellular communicating rami extend from the cervical spinal nerves, in mammalian (guinea-pig, pig) embryos toward the primordia of the sympathetic trunks through which cells advance into the latter He maintained that these cellular rami persist for a short time and then disappear, after which there are no connections between the cervical spinal nerves, except the last, and the sympathetic trunks until the gray communicating rami arise The writer has been unable to substantiate these observations of Ganfini either in porcine or human embryos He could obtain no evidence that cells enter the primordia of the cervical sympathetic ganglia via the cervical spinal nerves In both human and porcine embryos the primordia of the sympathetic trunks grow cephalad from the lower cervical region both by the displacement of cells along the dorsal aspects of the descending aortæ and by cell proliferation These primordia do not appear segmented in early embryos but remain continuous cell columns until segmentation of these columns takes place, resulting in the formation of the cervical sympathetic ganglia

The segmental character of the sympathetic trunks is apparent throughout the greater part of their extent in human embryos 10 mm in length The ganglionic primordia are more compact at this stage than in the earlier stages, but some cells of nervous origin still remain somewhat scattered and, although the ganglionic masses in adjacent segments are connected by longitudinal fibers, these connecting rami are nowhere free from cells As the curvature of the embryo becomes less marked with advancing development, the ganglia of the sympathetic trunks become more widely separated and more sharply delimited In human embryos 15 mm in length, the segmental character of the sympathetic trunks is well marked below the cervical region The segmentation of the cervical portion which results in the cervical sympathetic ganglia is also well advanced Fibers may now be traced cephalad from the superior cervical ganglia along the internal carotid arteries In embryos 20 to 22 mm in length, the ganglia of the sympathetic trunks have taken definite form and are sharply delimited the fibrous rami connecting them with one another are relatively free from cells, and the trunks have assumed a definite relationship to the vertebral condensations

Prevertebral Plexuses —The primordia of the ganglia of the abdominal prevertebral plexuses arise along the ventrolateral aspects of the aorta In the upper abdominal region of human embryos 6 mm in length, cells may be traced in small numbers from the primordia of the ganglia of the sympathetic trunks ventralward along the lateral aspects of the aorta The primordia of the ganglia of the sympathetic trunks in this region are not sharply delimited but cells apparently become detached from them and advance ventralward into the primordia of the prevertebral ganglia In embryos which are somewhat farther advanced, fibers may also be traced from the primordia of the thoracic sympathetic ganglia below the fourth or fifth thoracic segment toward the primordia of the prevertebral ganglia in the upper abdominal region These are mainly fibers which join the sympathetic trunks through the communicating rami of the thoracic nerves and continuing toward the prevertebral plexuses, give rise to the splanchnic nerves In human embryos 10 mm and over in length, the aggregates of cells which constitute the primordia of the prevertebral ganglia are conspicuous along the abdominal aorta Some cells have already become displaced from these cell masses toward the primordia of the adrenal glands and along the renal arteries The greatest accumulation of sympathetic cells ventral to the abdominal aorta occurs at the origin of the celiac artery The prevertebral plexuses are not yet clearly delimited, and fibers cannot be traced from their primordia into the mesentery The several plexuses become more clearly delimited as development advances and the ganglionic cell aggregates become more compact

Chromaffin System —The chromaffin system consists of the medullary portions of the adrenals and the paraganglionic bodies The latter are aggregates of chromaffin cells related to the sympathetic ganglia and located mainly along the abdominal aorta Human embryos exhibit a wide range of variation in the number of paraganglia and the quantity of chromaffin tissue outside the adrenal bodies (Zuckerkandl, 1901) Much of the chromaffin tissue outside the adrenals undergoes retrogressive changes during postnatal life but the paraganglia do not wholly disappear

Leydig (1853) regarded the adrenal bodies as an integral part of the sympathetic nervous system Balfour (1878) clearly differentiated the chromaffin tissue from the interrenal tissue in elasmobranch embryos and showed that the former is derived from the sympathetic primordia Wiesel (1901) and Whitehead (1903) concluded, on the basis of their studies of mammalian embryos, that the adrenal medulla is composed of cells which are displaced from the adjacent sympathetic primordia On the basis of extensive observations and a review of the literature, Poll (1906) advanced the opinion that the chromaffin tissue is composed of cells derived from the sympathetic primordia in all the vertebrates Most of the more recent investigators, including Kohno (1925), Da Kosta (1926), Iwanow (1925, 1927), Willier (1928) and Harman and Derbyshire (1932) have concurred in this opinion

The cells destined to become chromaffin cells cannot be differentiated from the other cells of nervous origin in the sympathetic primordia in early embryos They assume the characteristic appearance of chromaffin elements relatively late during embryonic development According to Soulié (1903), the displacement of cells from the adjacent sympathetic primordia into the adrenal capsules begins in human embryos about 19 mm in length The differentiation of cells of sympathetic origin into chromaffin cells and the formation of chromaffin bodies outside the adrenals is initiated at a somewhat earlier stage According to Iwanow (1927), chromaffinoblasts may be recognized in some human embryos, 11 5 mm in length although such cells may not appear in other embryos which are somewhat farther advanced Well organized chromaffin bodies are not found in human embryos until they have attained a length of about 30 mm The cells which make up the adrenal medulla according to Iwanow, are derived in part directly from the adjacent sympathetic primordia and in part from the chromaffin bodies along the abdominal aorta

The carotid body which at least in some animals, is made up in part of chromaffin tissue is situated at the bifurcation of the common carotid artery According to Kohn (1900), the chromaffin cells in this body are derived from the superior cervical sympathetic ganglion and the vagus nerve According to Smith (1924), these cells are derived from the cervical sympathetic primordia and the parasympathetic primordia in the head The cells from the latter primordia advance into the primordium of the carotid body along branches of the glossopharyngeal and vagus nerves The contribution of cells from each of these sources varies in different species In certain mammalian species, *e g*, the rat, the carotid body probably contains no chromaffin tissue

Plexuses Related to the Vagi —The cardiac and pulmonary plexuses and the enteric plexuses except in the distal parts of the intestine, arise from primordia composed of cells of cerebrospinal origin which are displaced distalward along the paths of the vagi This conclusion was *first* based on a study of mammalian (pig) embryos (Kuntz, 1909) and confirmed later by the results of studies based on embryos of types of the other classes of vertebrates

In early human embryos the vagus nerves, like the spinal nerves contain cells of nervous origin In favorable sections through the vagus roots continuous lines of cells of medullary origin may be observed extending from the wall of the hind-brain into these roots In sagittal sections

lines of cells also extend from the distal ganglion on the vagus nerve into the nerve trunk. Cells identical in appearance with those in the ganglia also are present in abundance in the more distal parts of the growing vagi. Vagus branches bearing small aggregates of such cells may also be traced toward the esophageal wall.

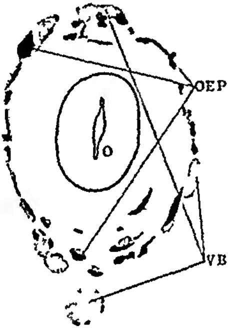


FIG. 30.—Esophageal plexus in transverse section, human embryo 10.1 mm. in length. O, Esophagus; OEP, cell masses in esophageal plexus; VB, vagus branches.

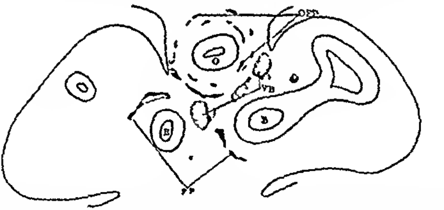


FIG. 31.—Esophageal and pulmonary plexuses in transverse section, human embryo 10.1 mm. in length. B, Bronchus; O, esophagus; OEP, cell mass in esophageal plexus; PP, cell masses in pulmonary plexuses; VB, vagus branches.

In embryos 6 mm. in length vagus branches may be traced to the stomach and for a short distance along its lesser curvature, toward the roots of the lungs and toward the bulbar region of the heart. Associated with all these branches are many cells of nervous origin. In embryos 7 to 9 mm. in length the pulmonary branches have reached the roots of the lungs and the cardiac branches may be traced close to the base of the heart. The latter branches are accompanied by numerous cells of nervous origin which tend to become aggregated near their growing tips and give rise to the primordia of the cardiac ganglia. The esophageal plexus is

already well formed over the dorsal aspect of the heart and comes into close proximity to the walls of the atria Vagus branches with their accompanying cell aggregates form a plexiform meshwork around the lower portion of the esophagus (Fig 30) Below the bifurcation of the trachea, vagus branches including cells of nervous origin may be traced into the roots of the lungs, where masses of such cells occur in proximity to the bronchi and the pulmonary vessels (Fig 31) These nervous complexes which constitute the primordia of the pulmonary plexuses are continuous with the esophageal plexus and with that portion of the cardiac plexus which is associated with the walls of the atria

In human embryos 7 to 9 mm in length, many cells of vagus origin have advanced into the wall of the esophagus but a definite concentric arrangement of these cells is not yet apparent In embryos 10 mm in length, vagus branches accompanied by migrant nerve cells may be traced along the wall of the stomach Many of these cells penetrate the stomach wall with the terminal vagus branches and become incorporated in the primordia of the enteric plexuses As development advances, the primordia of these plexuses also become apparent in the intestine As the cells of nervous origin in the wall of the digestive tube gradually become more numerous, they become aggregated in minute ganglionic masses which assume a concentric arrangement in two layers constituting the primordia of the myenteric and submucous plexuses

It is significant that no paths along which cells advance from the sympathetic trunks or prevertebral plexuses into the pulmonary, cardiac and enteric plexuses are established during the early stages of development The early development of the latter plexuses goes on simultaneously with that of the sympathetic trunks and prevertebral plexuses Sympathetic nerves grow into the cardiac and pulmonary plexuses later but not until the primordia of the ganglia of these plexuses are well established

On the basis of his early observations, the writer (1909) advanced the conclusion that the primordia of the enteric plexuses in the small intestine also are composed mainly of cells of vagus origin Abel (1912) supported this view on the basis of her findings in embryos of the chick On the contrary, Uchida (1927) advanced certain data which he interpreted as indicating the displacement of cells from the sympathetic primordia into the walls of the intestine before cells of vagus origin have advanced far enough to reach this part of the digestive tube He concluded that the primordia of the enteric ganglia in the intestine are composed mainly of cells of sympathetic origin and later also receive cells of vagus origin, although the primordia of the enteric ganglia in the esophagus and stomach are made up mainly of cells displaced distalward along the vagi Experimental data advanced by Jones (1942) support the assumption that the enteric ganglia throughout the small intestine comprise only cells which are displaced distalward along the vagi The enteric ganglia in the hindgut sustain a histogenetic relationship to the sacral nerves which is comparable to that which the ganglia in the more proximal divisions of the enteric canal sustain to the vagi

Cranial Autonomic Ganglia —*Ciliary Ganglion* —The primordium of the ciliary ganglion is composed of cells which are displaced distalward along the oculomotor and ophthalmic nerves The displacement of cells along the oculomotor nerve is not very apparent in early human embryos, but

some cells apparently of nervous origin are present in the nerve trunk In some embryos, an aggregate of intensely staining cells could be observed on the oculomotor nerve at the site of the primordium of the ciliary ganglion before cells could be traced to this point from the ophthalmic nerve The latter nerve has the appearance, in early human embryos, of a nerve along which cells are advancing distalward Continuous lines of cells identical with the cells in the semilunar ganglion extend from this ganglion along the ophthalmic nerve Cells also become aggregated very early in the path of this nerve at a point just proximal to the origin in the nasociliary ramus This aggregate of cells gradually extends toward the oculomotor nerve until it becomes continuous with the cell aggregate on

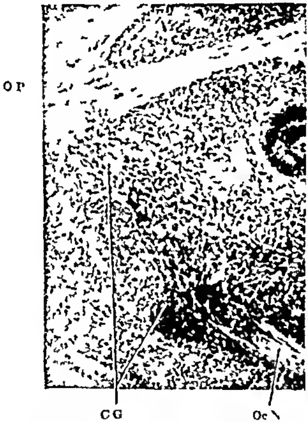


FIG 32 —Sagittal section through primordium of ciliary ganglion human embryo 14 mm in length *C G* Ciliary ganglion *Oc.N* oculomotor nerve *O P* ophthalmic nerve

the latter nerve (Fig 32) At this stage (14 mm), nerve fibers may be traced from the oculomotor nerve into the primordium of the ciliary ganglion As development advances, this ganglionic cell mass gradually becomes separated from the ophthalmic nerve but remains in contact with the oculomotor nerve until relatively late This aggregate of cells which includes the primordium of the ciliary ganglion is relatively large in early human embryos and most of its constituent cells appear to be derived from the semilunar ganglion but the number contributed via the oculomotor nerve is not insignificant On the basis of these observations, the ciliary ganglion appears to be genetically related to both the oculomotor and ophthalmic nerves This is in full accord with the findings of Carpenter (1906) in embryos of the chick Ganfini (1917) in embryos of various

vertebrates and Deery (1932) in embryos of the cat On the contrary Broman (1911) Streeter (1912) and Stewart (1920) described the ciliary ganglion as derived exclusively from the semilunar ganglion

In embryos of the chick, as reported by Jones (1942), the primordium of the ciliary ganglion is represented by a relatively large aggregate of cells in the path of the oculomotor nerve before any connections with the trigeminal nerve can be observed In his experiments, removal of the cephalic neural crests prevented the development of trigeminal ganglia but did not prevent the development of the primordia of the ciliary ganglia On the other hand removal of the mid-brain, including the oculomotor nuclei, but leaving the cephalic neural crests intact, did not prevent the accumulation of cells at the sites of the primordia of the ciliary ganglia

Sphenopalatine Ganglion —The primordium of the sphenopalatine ganglion arises at the growing tip of the greater superficial petrosal nerve as an aggregate of cells which are displaced distalward along this nerve It first becomes apparent in human embryos 10 to 11 mm in length The geniculate ganglion is not sharply delimited during early development Cells apparently become separated from it and advance along the path of the greater superficial petrosal nerve This nerve has the appearance, during early development, of a narrow migration pathway Many of the cells which are displaced along its course undoubtedly are cells of medullary origin

The primordium of the sphenopalatine ganglion lies medial to the maxillary nerve but not in contact with it In embryos 12 to 15 mm in length, rami of the maxillary nerve accompanied by cells derived from the semilunar ganglion may be traced into the sphenopalatine primordium Most of the cells in this primordium advance into it via the greater superficial petrosal nerve but it also receives cells from the semilunar ganglion via the maxillary nerve and its sphenopalatine rami Ganfini (1917) recognized a contribution of cells to the sphenopalatine ganglion via the greater superficial petrosal nerve in embryos of the guinea-pig and pig but did not regard it as sufficient to play a significant part in the development of this ganglion On the contrary, Stewart (1920) maintained, on the basis of his observations on embryos of the pig and the rat, that the primordium of the sphenopalatine ganglion contains only cells which are displaced distalward along the greater superficial petrosal nerve

Otic Ganglion —The primordium of the otic ganglion arises at the growing tip of the lesser superficial petrosal nerve as an aggregate of cells which are displaced distalward along this nerve It is first apparent in human embryos 9 to 10 mm in length In sagittal sections of embryos 8 mm in length the tympanic ramus of the glossopharyngeal nerve may be traced to the level of the geniculate ganglion Its fibers are accompanied by cells of nervous origin, giving it the appearance of an early migration path The primordium of the otic ganglion may usually be recognized when this ramus has reached a point a little below the level of the semilunar ganglion It increases in size rapidly and becomes elongated Its upper pole soon extends above the lower level of the semilunar ganglion and lies in close proximity to this ganglion During the early phases of its development the primordium of the otic ganglion is not connected with the semilunar ganglion but in embryos 13 mm and over in length it is apparent that cells derived from the semilunar ganglion become

incorporated in the primordium of the otic ganglion The otic ganglion now lies in contact with the proximal portion of the mandibular nerve This nerve, like the other divisions of the trigeminal, contains numerous cells of cerebrospinal origin some of which deviate from its course along the slender rami which join the otic ganglion Inasmuch as the mandibular nerve has a motor as well as a sensory root it is not unprobable that a portion of the cells which advance distalward along its course are derived directly from the hind-brain but it is quite apparent that many of the cells of trigeminal origin which enter the otic ganglion are derived directly from the semilunar ganglion Broman (1911) and Streeter (1912), who studied the development of the otic ganglion in human embryos and Camfini (1917), who studied it in embryos of the pig and guinea pig supported the theory that the cells which give rise to this ganglion are derived exclusively from the semilunar ganglion On the contrary Stewart (1920), who studied preparations of embryos of the pig and the rat, maintained that the otic ganglion arises solely from cells which are displaced distalward along the lesser superficial petrosal nerve

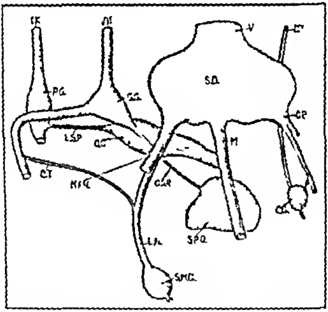


FIG 33 —Diagrammatic reconstruction of the larger cranial autonomic ganglia and the nerves to which they are genetically related in a human embryo about 20 mm in length *C G* Ciliary ganglion *C T* chorda tympani *G G* geniculate ganglion *G.S.P.*, greater superficial petrosal nerve *L.N* lingual nerve *L S I* lesser superficial petrosal nerve *M* maxillary nerve *MAN* mandibular nerve *O G* optic ganglion *OP* ophthalmic nerve *P G* petrosal ganglion *S G* Gasserian ganglion *S M G* submaxillary ganglion *SP G.*, sphenopalatine ganglion

Submaxillary Ganglion —The primordium of the submaxillary ganglion arises in human embryos 10 to 11 mm in length as an accumulation of cells in the path of the lingual division of the mandibular nerve In view of the developmental relationship of the other cranial autonomic ganglia to the nerves which convey their preganglionic fibers, we should expect to find cells of facial origin displaced into the primordium of the submaxillary ganglion along the chorda tympani This branch of the facial, however, does not join the lingual nerve until the primordium of the submaxillary ganglion has attained considerable size Cells which advance from the

facial nerve along the chorda tympani probably enter the primordium of the submaxillary ganglion during its later development, *i e*, after the junction of the chorda tympani with the lingual nerve is effected, but the cells which enter this primordium early are cells of trigeminal origin, some of which probably advance directly from the hind-brain along the motor root of the mandibular nerve Most of the cells which enter the submaxillary ganglion obviously are of trigeminal origin This is in full accord with the findings of Broman (1911) and Streeter (1912) in human embryos Ganfini (1917) advanced the opinion, based on his findings in embryos of the pig and guinea pig that the submaxillary ganglion arises solely from cells of trigeminal origin On the contrary, Stewart (1920) concluded that the submaxillary ganglion arises exclusively from cells which are displaced along the chorda tympani, although he admitted that, by reason of the intimate relationship of the primordium of this ganglion with the lingual nerve direct observations lend little support to this conclusion

Sublingual and Lingual Ganglia —The primordium of the sublingual ganglion arises as an accumulation of cells in the path of the lingual nerve somewhat distal to the primordium of the submaxillary ganglion Cells of nervous origin also advance along the branches of the lingual nerve and give rise to small ganglionic masses in the tongue These minute ganglia remain associated with the branches of the lingual nerve The cells which give rise to the sublingual ganglion and the smaller ganglia in the tongue associated with the branches of the lingual nerve obviously are derived from the same sources as those which give rise to the submaxillary ganglion

Minute ganglia also occur in the posterior portion of the tongue They are associated with the lingual ramus of the glossopharyngeal nerve and probably include only cells which are displaced distalward along this nerve As the glossopharyngeal nerve grows into the tongue, groups of cells accumulate near its growing extremity Some of these cell groups remain closely associated with the nerve trunk, others give rise to minute ganglia throughout the portion of the tongue which is innervated by the glossopharyngeal nerve

Histogenetic Relationships —The assumption that the cells which become differentiated into ganglion cells in the ganglia of the sympathetic trunks and the prevertebral plexuses are derived from the neural tube via the ventral roots of the spinal nerves represents a wide departure from the older teaching but is in full accord with our present knowledge of the functional relationships of the sympathetic system The neurons in the ganglia of the sympathetic trunks and prevertebral plexuses are commonly regarded as efferent in function In the central nervous system, efferent neurons arise mainly in the ventral or basal plate and afferent neurons mainly in the dorsal or alar plate, consequently it seems more probable that the sympathetic neurons are derived from the ventral portion of the neural tube, which is a source of efferent neurons, than from the spinal ganglia or neural crest which is a source of afferent neurons Certain investigators, particularly E Muller and Ingvar (1923) and Van Campenhout (1929 1930), have maintained that the sympathetic primordia are composed of cells which are derived exclusively from the spinal ganglia or neural crests They contended that no cells of medullary origin become displaced into the ventral roots of the spinal nerves

The existence of cells of medullary origin in the ventral spinal nerve

roots has been reported in embryos of all classes of vertebrates The evidence that these cells are displaced from the ventral part of the neural tube via the ventral nerve roots is especially clear in elasmobranch embryos Balfour (1877) described the early ventral nerve root in these embryos as "an elongate cellular structure with a wide attachment to the spinal cord" His illustrations indicate continuity of this cellular structure with the mantle layer in the wall of the neural tube This condition is illustrated in Figure 34, taken from a cross section of an embryo of S acanthias in our collection Continuous lines of cells extending from the mantle layer of the neural tube into the ventral nerve roots may also be observed occasionally in preparations of embryos of birds and mammals This condition as observed in preparations of an embryo of the chick, is illustrated in Figure 35 Individual nuclei partly within and partly without the external limiting membrane in the ventral roots of the spinal nerves and the motor roots of the cranial nerves occur not uncommonly in preparations of embryos of all the higher vertebrates including the human species

Fig 34 —Section through the ventral root of a spinal nerve in an embryo of Squalus acanthias A column of cells of medullary origin extends into the nerve root.

Most of the more recent investigators who have studied the development of the autonomic nervous system or any of its parts, particularly Abel (1912), Ganfini (1911–1918) Stewart (1920), Rau and Johnson (1923), Goormaghtigh (1924), Uchida (1927) Deery (1932) Raven (1937) Von Mahalik (1940) and Jones (1937–1942), have emphasized the importance, in the establishment of the primordia of the autonomic ganglia of the cells of medullary origin which are displaced distalward along the efferent nerve roots

In an investigation undertaken to determine more exactly the role of cells of medullary origin in the development of the sympathetic ganglia embryos of the chick were subjected to an operative procedure before the close of the second day of incubation, by which a part or all of the nervous tissue was destroyed throughout a series of segments These embryos were killed about the close of the fifth day of incubation and prepared for study (Kuntz 1922 1923)

In some of these embryos as became apparent on microscopic examina

tion of the sections, the spinal ganglia and dorsal nerve roots were absent on one or both sides through a series of segments, while the ventral portion of the neural tube remained intact and the ventral nerve roots were apparently of normal size. In other embryos, nearly all the nervous tissue was destroyed in a series of segments, leaving only a small ventral portion of the neural tube intact. In nearly all these cases ventral nerve roots were present but diminished in size in proportion to the degree of destruction of the basal plate of the neural tube. Visceral rami were present wherever a part or all of the portion of the mantle layer which gives rise to the intermediolateral cell column remained intact but absent wherever this portion of the mantle layer was completely destroyed. Preparations of embryos in which all the nervous tissue was destroyed throughout a series of segments showed no traces of spinal nerves in these segments.

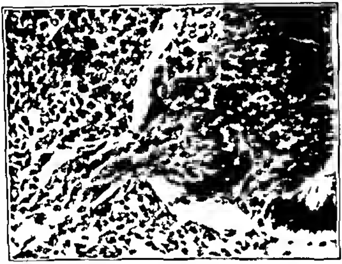


FIG. 35.—Section through the ventral root of a spinal nerve in an embryo of the chick about the close of the fourth day of incubation. Cells of medullary origin are present in the ventral nerve root.

An aggregate of cells representing the sympathetic primordium was present in every instance in which there was a ventral nerve root with a visceral ramus, even though there was no spinal ganglion or dorsal nerve root; but no sympathetic primordium was observed in any segment in which there was no visceral ramus, even though there was a small ventral nerve root, except in one instance in which very small sympathetic primordia were present in the upper thoracic segments in complete absence of spinal ganglia and neural tube in these segments. Some cells obviously were displaced peripheralward in the segments in question in this embryo before it was subjected to operation. Sections through the lower thoracic segments in the same embryo revealed no sympathetic primordia, since the peripheral displacement of cells of nervous origin was not yet initiated in the lower thoracic segments. Most of the preparations used showed no evidence of the peripheral displacement of cells of neural crest origin before the operative procedure was carried out.

Van Campenhout (1929, 1930), as stated above, denied the displacement of cells of medullary origin distalward along the efferent nerve roots but maintained that the cells of nervous origin which enter the primordia of the autonomic ganglia are derived exclusively from the neural crests.

In criticizing our findings he said "A more careful study of serial sectio would have shown him that the few sympathetic ganglia found in th segment without spinal ganglia only represent the extension for a sho distance of the sympathetic structures connected with the spinal nerve two or three segments above or below." The validity of this criticism cannot be admitted since Jones (1937) has shown that cells in the sympa thetic primordia do not migrate from more caudal segments into adjacent segments from which the neural tube has been removed and that such cells do not migrate caudalward more than three segments from segments farther cephalad.

The theory that the primordia of the autonomic ganglia include on cells of neural crest origin does not take account of the cells of medullar origin which are displaced into the efferent nerve roots. The positi findings of all the investigators cited above who observed and illustrate (in some instances photographically) the continuity of cell columns extend ing from the mantle layer of the neural tube into the efferent nerve roots or individual cells in the efferent roots partly within and partly without the external limiting membrane cannot be invalidated by the negative findings of a few investigators particularly if such negative findings pertain to amphibian species in which the autonomic ganglia admittedly are but poorly developed.

In the light of our findings in experimental embryos of the chick and th more recent experimental studies particularly those of Jones, we cannot avoid the conclusion that the primordia of the ganglia of the sympathetic trunk may arise in complete absence of spinal ganglion or neural crest cells. Under these conditions the cells composing the sympathetic primordia must be derived exclusively from the neural tube via the ventral spinal nerve roots. The fact that such primordia do not arise in segments in which the portion of the mantle layer which gives rise to the intermedio-lateral cell column is destroyed even though a small ventral nerve root is present suggests that the cells which enter the sympathetic primordia via the ventral nerve roots under normal conditions are derived mainly from this portion of the neural tube.

Cells which become displaced from the spinal ganglia undoubtedly enter the sympathetic primordia under normal conditions. The ultimate fate of the cells of medullary and ganglionic origin respectively in the sympathetic primordia cannot be determined by the microscopic study of embryonic material. Froriep's opinion that the sympathetic neurons a derived mainly from cells of medullary origin was based on the assumption that the sympathetic neurons are efferent and that the basal plate of th neural tube is the chief source of efferent neurons. Inasmuch as many o the cells of nervous origin which advance peripheralward become differ entiated into neurilemma cells the cells of spinal ganglion origin which become incorporated in the sympathetic primordia could be accounted for without assuming that they become differentiated into sympathetic neurons.

According to the concept based on Harrison's (1904, 1906, 1924) studies which has been most widely prevalent, neurilemma cells are derived mainly from the neural crests although the medullary origin of some is not precluded. On the basis of experimental studies carried out o amphibian embryos in which the neural crests and the neural tube were

differentially stained with vital dyes, Detweiler (1937) advanced the opinion that the earliest neurilemma cells are derived from the neural crests, but some of the later ones may be derived from the neural tube. On the basis of transplantation experiments in which tadpoles of two amphibian species were utilized, Raven (1937) concluded that, in these species, neurilemma cells are derived exclusively from the neural tube. The results of studies associated with his experimental investigation of the origin of autonomic ganglion cells led Jones (1939) to conclude that the neurilemma cells associated with the fibers of the dorsal spinal nerve roots are derived from the neural crests and those associated with the fibers of the ventral spinal nerve roots are derived from the neural tube. In segments in which the neural crests had been removed, so that spinal ganglia failed to develop but ventral nerve roots were present, he always found neurilemma cells associated with the ventral root fibers, unless the material was fixed too early. He has shown that differentiation of neurilemma in the ventral nerve roots is delayed in embryos which have been subjected to operative removal of the neural crests, due to the retarding effect of the operation on the migration of cells of medullary origin into the ventral nerve roots. The ventral root fibers, therefore, are, for a time, devoid of neurilemma.

Although the neurilemma cells associated with the fibers of the ventral spinal nerve roots are not derived from the neural crests, the cells of neural crest origin which become displaced into the primordia of the sympathetic ganglia can still be accounted for without assuming that any of them become differentiated into ganglion cells, since nearly all sympathetic ganglia are traversed by dorsal root fibers. The possible rôle of neural crest cells in the interstitial structure of the autonomic ganglia, furthermore, as yet is not fully known. The assumption that sympathetic ganglion cells arise exclusively from cells of medullary origin, therefore, is not incompatible with the fact that cells of neural crest origin are displaced into the sympathetic primordia.

The parasympathetic ganglia sustain a histogenetic relationship to the nerves which include the parasympathetic preganglionic outflow comparable to that of the sympathetic ganglia to the thoracic and upper lumbar spinal nerves. The conclusion advanced by Kuntz on the basis of extensive studies of preparations of normal embryos of species of all classes of vertebrates that the thoracic prevertebral ganglia and the enteric ganglia except in the distal portion of the enteric canal, are made up of cells which are displaced distalward along the vagus nerves has been corroborated by the finding reported by Jones (1942) that these ganglia fail to arise in embryos of the chick in which the hind brain had been removed at approximately the forty-second hour of incubation. Jones also reported that the ganglion coli and the enteric ganglia in the distal portions of the enteric canal failed to arise in embryos in which the caudal portion of the neural tube was removed at the forty-eighth hour of incubation. This experimental finding supports the assumption that the cells which become differentiated into ganglion cells in the distal portion of the enteric canal are displaced distalward from the sacral segments of the neural tube along the sacral nerve roots.

Segregation of the cells of medullary origin from those of sensory ganglion origin along the paths of the vagus, glossopharyngeal and facial nerves is

beset with peculiar difficulties. The sensory ganglia associated with these nerves are not derived exclusively from the neural crests. Consequently, they cannot be eliminated by removal of the cephalic portions of the latter structures alone. Since these ganglia are traversed by the preganglionic components of the respective nerves, their removal after complete differentiation of their primordia can hardly be accomplished without damage to the preganglionic outflow. Removal of the portions of the hind brain which include the efferent nuclei of these nerves without destroying the primordia of the sensory ganglia probably can be accomplished.

In the experiments on chick embryos reported by Jones (1942) in which the hind brain and the corresponding portions of the neural crests were removed at the forty-second hour of incubation, this operation did not prevent the development of the nodose ganglion of the vagus nerve. Fibers growing cephalad and caudad from this ganglion also were present. The former did not grow into the residue of the brain stem. The latter may be traced into the wall of the stomach but there are no neuroblasts associated with them. The nodose ganglia obviously contribute no neurons to the parasympathetic ganglia related to the vagus nerves. The parasympathetic ganglia probably sustain a histogenetic relationship to the brain stem and the sacral segments of the spinal cord comparable to that of the sympathetic ganglia to the thoracic and upper lumbar spinal cord segments.

The concept of the development of the autonomic nervous system here set forth does not imply that all the cells which become differentiated into neurons in its ganglia actually migrate from the neural tube. In a critical study of cell differentiation in the central nervous system, Schaper (1897) pointed out that the cells which arise by the mitotic division of the "germinal" cells in the ependymal layer do not all become neuroblasts. He described them as "indifferent" cells, some of which become differentiated into neurons and others into neuroglia. He also pointed out that in the higher vertebrates many of the indifferent cells retain the capacity for further propagation by mitotic division and give rise to daughter cells of the same indifferent type which may become differentiated either into neurons or supporting cells. Most of the cells of nervous origin which are displaced distalward along the cranial and spinal nerves conform to Schaper's description of the indifferent cells. In preparations of embryos which are sufficiently advanced in their development, a neuroblast may be observed occasionally along the path of migration but most of the cells which develop into neurons in the autonomic ganglia cannot be identified as neuroblasts until they have entered the primordia of these ganglia. Many migrant cells, apparently of the indifferent type, do not become differentiated into neuroblasts but give rise to neurilemma. In preparations of early embryos of the higher vertebrates, mitotic figures occur not infrequently in both the nerve trunks and the autonomic primordia. It may be assumed, therefore, that many of the cells which become differentiated into neurons in the autonomic ganglia arise by the mitotic division of migrant cells either before or after they have become incorporated in the primordia of these ganglia. The neurons in the autonomic system consequently, may be regarded as homologous with the neurons in the cerebrospinal nervous system.

The cells in the autonomic primordia which are destined to become ganglion cells do not differentiate simultaneously or at the same rate. Preparations of ganglia taken from human fetuses during the sixth or seventh month of gestation show cells in all phases of differentiation from bipolar or unipolar neuroblasts to young multipolar ganglion cells of large sizes. The earliest dendritic processes at first are unbranched but branching is initiated relatively early and continues for an indefinite period. The dendrites of individual ganglion cells which arise earliest, according to de Castro (1932), are longer and of greater diameter than those which arise later. Consequently, they may be recognized in the adult as the primary dendritic processes. Many of the short dendrites arise relatively late.

CHAPTER VII

INNERVATION OF THE HEART

Extrinsic Nerves —The heart is innervated through the sympathetic cardiac nerves, the cardiac branches of the vagi and the cardiac plexus. The sympathetic innervation of the heart includes the superior, middle and inferior cardiac nerves arising from the superior, middle and inferior cervical sympathetic ganglia respectively, and several rami which arise from the sympathetic trunk below the inferior cervical or stellate ganglion. The latter were not included in the earlier accounts of the innervation of the mammalian heart. Valentin (1843) described nerves passing from the second thoracic sympathetic ganglion into the cardiac plexus in man but little attention was given to his account until thoracic sympathetic cardiac nerves were described by several more recent investigators. Perman (1924) described nerves passing from the sympathetic trunk as low as the fourth thoracic segment on the left and the sixth thoracic segment on the right side to the heart in the calf. Cannon *et al* (1926) found that complete elimination of the cardiac accelerators in the cat by extirpation of the sympathetic trunks requires removal of the sympathetic ganglia as low as the sixth or seventh thoracic segments. According to Ionescu and Enachescu (1928), thoracic cardiac nerves arise from the second to the fifth thoracic segments of the sympathetic trunks in man. Kuntz and Morehouse (1930) have verified these findings both in adult and young human cadavers and still born fetuses. In all the cadavers examined by them nerves could be traced from the medial aspects of both the second and third thoracic ganglia or the interganglionic portions of the sympathetic trunk in the second and third thoracic segments. These nerves commonly unite forming a single trunk which passes medialward and downward and gives rise to branches some of which join one or more of the cervical sympathetic cardiac nerves and cardiac branches of the vagi while others enter the cardiac plexus directly. A nerve arising from the fourth thoracic sympathetic ganglion joins the cardiac plexus and also gives off slender branches to the pulmonary and esophageal plexuses, particularly on the right side. In most of the cadavers examined slender nerves could also be traced from the fifth and sixth thoracic ganglia of the sympathetic trunk toward the aorta bilaterally. As observed by Saccomanno (1943) in human material, nerves may be traced from the upper six or seven thoracic sympathetic trunk ganglia and internodes into the cardiac plexus. Such nerves are more abundant in the fourth and fifth thoracic segments than at higher levels. Thoracic nerves, according to his observations, comprise approximately twice as many nerve fibers which enter the cardiac plexus as the cervical sympathetic cardiac nerves.

The parasympathetic innervation of the heart commonly involves three rami of the vagus nerve on either side. The superior cervical ramus arises from the vagus trunk just distal to the origin of the superior laryngeal nerve. The inferior cervical, the largest cardiac ramus of the vagus usually arises from the recurrent nerve. The third or thoracic cardiac ramus arises from the vagus trunk within the thorax. The efferent com

ponents of the sympathetic cardiac nerves are postganglionic fibers which arise from cells located in the sympathetic ganglia from which the nerves arise. The corresponding preganglionic fibers are components of the upper thoracic nerves down to and including the fifth. The efferent components of the vagus branches to the heart are preganglionic fibers which terminate in synaptic relationship to ganglion cells in the cardiac

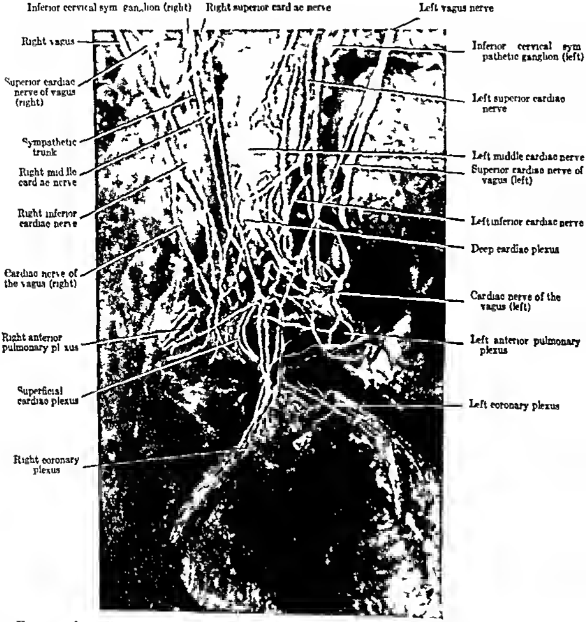


FIG 36 — Photograph of a dissection of the nerves to the heart in the human cadaver (By permission of Dr J D Humber)

plexus. Most of the preganglionic vagus fibers (70 to 80 per cent, according to Glaser, 1924) are unmyelinated. As the vagus fibers approach the cardiac plexus they mingle with the cardiac sympathetic fibers, a large percentage of which also is unmyelinated. There are no morphological criteria by which the fibers of vagus and sympathetic origin can be certainly identified within the cardiac plexus, unless they have been differentially stained. By the use of appropriate silver technic, according to Nonidez

(1939), the vagus fibers become more heavily impregnated than the sympathetic, particularly in young animals

With the exception of the superior sympathetic cardiac nerves which probably are devoid of afferent fibers, all the extrinsic nerves of the heart convey both efferent and afferent fibers The afferent fibers in the sym

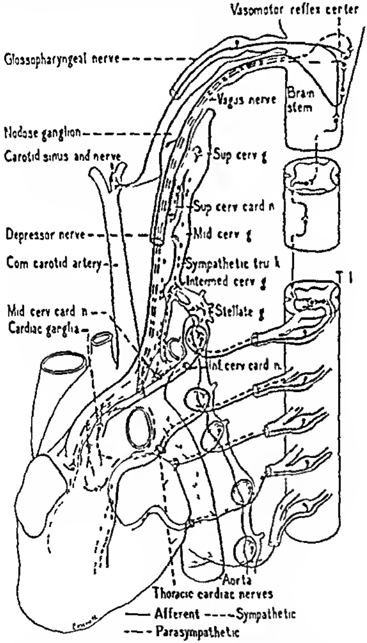


FIG 37 —Diagrammatic illustration of the sympathetic parasympathetic and afferent innervation of the heart (Kuntz 1944)

pathetic nerves, like the corresponding preganglionic fibers are components of the upper thoracic nerves The so-called depressor nerve is a branch of the vagus consisting mainly of afferent components which terminate in the proximal parts of the aorta and the adjacent cardiac wall

The Cardiac Plexus —Location and Distribution —The cardiac plexus is situated at the base of the heart and is composed of a superficial and a

deep part The superficial cardiac plexus lies superficial to the pericardium in the concavity of the aortic arch It is made up largely by the left superior sympathetic cardiac nerve and the inferior cervical cardiac branch of the left vagus These nerves approach the heart by passing over the arch of the aorta and meet on the right side of the ligamentum arteriosum At this point there usually is a small ganglion, the cardiac ganglion of Wrisberg

The deep cardiac plexus is situated behind the arch of the aorta and in part between the aorta and pulmonary veins It is a large plexus consisting of two lateral parts joined together by numerous fibrous communications These two parts are unlike in composition and distribution The one on the right side receives contributions from the right superior, middle and inferior cervical and thoracic sympathetic cardiac nerves and all the cardiac branches of the right vagus The one on the left side receives contributions from the left middle and inferior cervical and thoracic sympathetic cardiac nerves and the superior cervical and thoracic cardiac branches of the left vagus Thus, all the extrinsic nerves which contribute to the innervation of the heart except the inferior cervical cardiac branch of the left vagus and the left superior sympathetic cardiac nerve, enter the deep cardiac plexus It also receives communications from the superficial cardiac plexus

The superficial cardiac plexus sends branches of distribution along the pulmonary artery to join the anterior (right) coronary plexus It also sends branches of communication along the left branch of the pulmonary artery to the anterior pulmonary plexus and between the aortic arch and the bifurcation of the pulmonary artery to the left portion of the deep cardiac plexus

The right portion of the deep cardiac plexus contributes largely to the right or anterior coronary plexus The latter also receives fibers from the superficial cardiac plexus It supplies the substance of the heart along the course of the right coronary artery The right portion of the deep cardiac plexus also contributes to the posterior coronary plexus and communicates with the right anterior pulmonary plexus Reinforced by fibers from the superficial cardiac plexus, the left portion of the deep plexus gives rise to the left or posterior coronary plexus which supplies the substance of the heart along the course of the left coronary artery This portion of the deep cardiac plexus also contributes to the left anterior pulmonary plexus

The deep cardiac plexus in man has been further subdivided, particularly by Worobiew (1917), into six more or less distinct plexuses, the anterior and posterior atrial and the right and left anterior, and right and left posterior ventricular plexuses Corresponding subdivisions of the deep cardiac plexus have been described by Wollhynski (1928) in the calf Anufriew (1928) in the cat and Schurawlew (1928) in the dog According to these authors, the plexuses named above are constant components of the cardiac nerve supply, although they anastomose freely with one another and vary within relatively wide limits in different individuals Beneath the epicardium the larger nerve trunks accompany the coronary vessels Smaller nerves deviate from these usually at right angles to the courses of the vessels and form a simple subepicardial network The fibers of these nerves interlace in a complex manner beneath the epicardium both in the atria and ventricles Many of them come into relation to ganglion

cells, others penetrate the myocardium. Some of the latter reach the subendocardial tissue where they form a plexus.

Distribution of Cardiac Ganglia.—The intrinsic innervation of the heart has been studied by not a few investigators but there is no general agreement regarding the number and distribution of nerve fibers in the several layers of the cardiac wall. These studies are beset with technical difficulties. Probably the most satisfactory preparations have been obtained by the use of the intra vitam methylene blue technic. Silver impregnation methods have yielded satisfactory results in the hands of certain investigators. Differences in technic have played a large part in the interpretation of the histological findings.

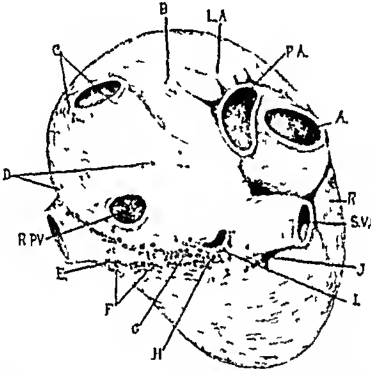


FIG. 38.—Distribution of ganglia at the base of the heart of a human fetus. *A*, Aorta. *B*, ganglia in the sulcus between the left atrium and left auricle. *C*, ganglia at the mouth of the pulmonary vein. *D*, ganglia in the esophageal sulcus of the left atrium. *E* and *F*, ganglia in the caudal portion of the sulcus terminalis. *G*, ganglia in the interatrial septum. *H*, ganglia in the sulcus terminalis. *I*, ganglia at the mouth of the right superior pulmonary vein. *J*, superior group of ganglia in the sulcus terminalis. *O.A*, left auricle. *R.P.V*, right pulmonary vein. *S.V.C*, superior vena cava. (Redrawn from Francillon.)

Ganglia have been reported in all parts of the heart in mammals, including man, and in lower vertebrates. The results of most of the more recent investigations indicate a limited distribution of cardiac ganglia. Perman (1924), who investigated 30 human hearts, found numerous ganglia on the posterior surface of the atria and the roots of the great vessels. These ganglia, according to his findings, are always interpolated in the nerve trunks. He divided them into two groups: one in proximity to the aorta and pulmonary artery and extending to the proximal ventricular wall, the other on the posterior surfaces of the atria and extending to the proximal parts of the ventricles. The first group is associated with the nerves which pass ventral to the transverse sinus and supply the ventral surface of the heart, the other is associated with the nerves which pass behind the

transverse sinus to supply the atria and the greater part of the dorsal surfaces of the ventricles Woollard (1926), who combined intra vitam methylene blue staining and the process of clearing used in the Spalteholtz method, studied transparent preparations of the superficial layers of the entire heart, including the visceral pericardium and a stratum of the underlying muscle of various vertebrates, including the snake, rabbit, cat and dog He described ganglia in abundance on the anterior and posterior surfaces of the left atrium and extending to both auricular appendages, a chain of ganglia extending along the interatrial septum, several large ganglia in the region of the atrio-ventricular sulcus, numerous smaller ones adjacent to the base of the pulmonary artery and along the proximal portion of its course No ganglia were found on the ventricular side of the

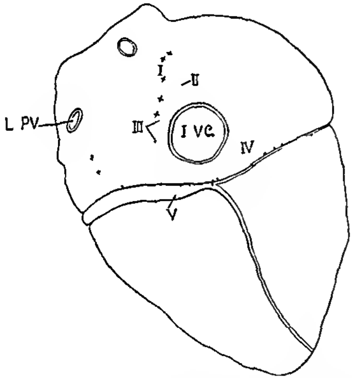


FIG 39—Distribution of ganglia on the diaphragmatic aspect of the heart of a human fetus *I* Ganglia in the interatrial septum *II* ganglia in the sulcus terminalis *III* ganglia in the wall of the right atrium ganglia adjacent to the mouth of the inferior vena cava (*I V C*) *L P V* left pulmonary vein *V* projection of the mouth of the coronary sinus in the right atrium (Redrawn from Francillon)

atrio-ventricular sulcus, except in the heart of the snake, where collections of ganglia occur in the region of the posterior interventricular sulcus Anufriew (1928) and Schurawlew (1928) also observed no ganglia in the ventricular walls in the cat and dog King (1939) reported some ganglia in the ventricular wall in the rat near the atrio-ventricular junction and small groups of ganglion cells close to the apex of the left ventricle In the light of all the evidence available at present, it appears that ganglion cells occur only rarely, if at all, in the ventricular walls in the hearts of most mammals

The intramural cardiac ganglia vary greatly in size The larger ones may be observed macroscopically in transparent preparations The smaller ones can only be detected microscopically According to the findings of

Francillon (1928) in an advanced human fetus, these ganglia contain 8 to 150 ganglion cells. They lie mainly in the subepicardial connective tissue. Although some lie deeper than others, various investigators including Perman, Woollard and Francillon, observed none which could be regarded as intramuscular. Okamura (1929, 1930) and King (1939) reported the occurrence of ganglion cells in the subendocardial tissue and in the myocardium. The distribution of the intramural cardiac ganglia as observed by Francillon, is illustrated in Figures 38 and 39.

Cardiac Ganglion Cells.—The ganglion cells in the ganglion of Wrisberg, according to Müller (1910), are morphologically similar to those in the sympathetic trunk ganglia. Most of them are relatively large. In general the cardiac ganglion cells are comparable to those in the intramural ganglia of other viscera, *e. g.* the enteric ganglia. They comprise ganglion cells with only short dendrites, ganglion cells with only long dendrites and ganglion cells with both long and short dendrites. According to de Castro (1932), ganglion cells with numerous short, frequently branching dendrites are very common. Those of adjacent cells frequently terminate in dendritic brushes in which some branches of long dendrites also terminate. The ganglion cells with only long dendrites usually show 5 to 10 of these processes which branch infrequently. They commonly terminate within the same ganglion in pericellular nests or dendritic brushes or glomeruli. Some extend into adjacent ganglia. The ganglion cells with both long and short dendrites vary widely with respect to the numbers of their processes. Many of the short ones terminate close to the cell bodies. The axons of the cardiac ganglion cells very commonly arise from axon hillocks on the proximal portions of dendrites.

Terminations of Incoming Fibers.—As the extrinsic nerves enter the cardiac plexus the fiber bundles gradually undergo changes in composition as they subdivide, intermingle with one another and enter the cardiac ganglia. The cardiac branches of the vagi comprise preganglionic and visceral afferent components most of which are myelinated. The sympathetic cardiac nerves comprise postganglionic fibers some of which are myelinated and visceral afferents which are mainly myelinated. Components of the vagus and sympathetic nerves, therefore, cannot be identified on the basis of their condition with respect to myelinization. In general, preganglionic fibers are larger than postganglionic ones, but this does not afford a useful criterion, since many of the vagus fibers are actually smaller than the largest of the sympathetic fibers. There are no known morphological criteria by which pre- and postganglionic fibers can certainly be separated from one another in the terminal plexuses. Woollard's observations afford some useful information bearing on this problem. He recognized three distinct types of fibers in the nerves entering the cardiac plexus. Some are myelinated and exhibit nodes of Ranvier. These may be regarded as visceral afferent. The depressor nerve includes fibers of this type. Some unmyelinated fibers with smooth contour may be traced into the cardiac ganglia. The preganglionic character of these fibers is strongly suggested. On the other hand, fibers of this type may often be identified as arising from cells in the cardiac ganglia. These obviously are postganglionic. As they approach their terminal distribution they become exceedingly fine and exhibit the varicosities characteristic of postganglionic fibers. The third group consists of varicose fibers of very

much smaller caliber than the other two types. Fibers of this type were observed in the incoming nerves and throughout those of the cardiac plexus. They probably are postganglionic. They are greatly reduced in numbers in the incoming nerves following extirpation of the stellate ganglia. This observation suggests that they are components of the sympathetic nerves but affords no conclusive evidence that no components of the cardiac nerves arising from the sympathetic trunks make synaptic connections in the cardiac ganglia. The latter possibility appears to be precluded by the findings of Lawrentjew (1929) in preparations of the heart following degenerative section of the vagus nerves. Woollard observed no alterations in the intraganglionic fiber terminations in the cardiac plexus or changes in the cardiac ganglion cells following removal of a large percentage of the sympathetic fibers by extirpation of both stellate ganglia. The results of the studies of both Lawrentjew and Woollard seem to indicate that only fibers of vagus origin effect synaptic connections in the cardiac ganglia. These ganglia, therefore, may be regarded as wholly parasympathetic.

The modes of termination of the preganglionic fibers in the cardiac ganglia fall broadly into two types, the pericapsular and the pericellular. As the incoming fibers which form the pericapsular terminations break up into their terminal branches, the latter become varicose and are applied to the capsule of the ganglion cell. In the pericellular terminations, the terminal branches of the incoming fibers are applied to the cell bodies and dendrites. The ganglion cells with pericapsular terminations are usually stained less intensely, in methylene blue preparations, than those with pericellular terminations. When the dendrites are relatively long, the terminal branches of the preganglionic fibers not infrequently twine around them throughout the greater part of their length. Not uncommonly preganglionic fibers may be seen to divide in various ways and to effect synaptic connections with a number of ganglion cells.

Terminal Distribution of Nerve Fibers.—*Efferent.*—The distribution of nerve fibers in the heart and their modes of termination have been described by various investigators. An abundant nerve supply to all parts of the heart is generally conceded, but there is no general agreement regarding the terminal structures in the cardiac musculature and the relative importance of the sympathetic and parasympathetic components.

An abundant plexus composed chiefly of unmyelinated fibers is present in the subepicardial tissue in all parts of the heart. The intracardiac ganglia are associated with this plexus. It is most abundant in the areas of distribution of the ganglia and throughout the interatrial septum. Fiber bundles arising from it penetrate the musculature and ramify throughout the myocardium, forming a loose meshwork between the fascicles of muscle cells and around them. A relatively rich plexiform meshwork occurs also in the subendocardial tissue, from which offsets actually penetrate the endocardium. Both the parietal and visceral pericardia are innervated through a moderate number of relatively slender bundles of nerve fibers. According to Glaser (1924), the nerves in the pericardium are made up largely of unmyelinated fibers but include myelinated fibers in small numbers. He found no ganglion cells either in the parietal or the visceral pericardium.

In transparent preparations of the hearts of cats and guinea-pigs,

Woollard traced nerve fiber bundles along the posterior surface of the left atrium which bear no ganglia and receive no fibers derived from ganglia in the cardiac plexus. These bundles probably are composed of sympathetic fibers which reach the ventricular wall without interruption in ganglia. In no instance could he trace fibers directly from the ganglia into the ventricles. Both fibers of sympathetic origin and fibers derived from cardiac ganglia could be traced into the atrial walls.

As stated above, small varicose fibers are more abundant in the sympathetic cardiac nerves than in the cardiac branches of the vagi. The axons of the cardiac ganglion cells also become varicose toward their terminal ends; therefore, it is impossible to differentiate between the fibers of sympathetic and those of parasympathetic origin in the terminal branches of the cardiac plexus on the basis of caliber and varicosity. After degeneration of the severed sympathetic fibers, following extirpation of both stellate ganglia, the distribution and abundance of fibers is altered much more profoundly in the ventricles than in the atria. The intramuscular plexus, so prominent in Woollard's preparations of normal ventricular muscle, could hardly be demonstrated in preparations of the ventricles of the operated animals. His findings strongly suggest that the atria and the atrio-ventricular bundle are supplied by both sympathetic and parasympathetic fibers, the ventricular muscle mainly by sympathetic fibers. According to Blair and Davis (1935), the entire atrio-ventricular conducting system is abundantly supplied with unmyelinated nerve fibers. In silver preparations of the hearts and adjacent structures in very young animals (cats, dogs) Nonidez (1939) found that the preganglionic components of the vagi and the axons of the cardiac ganglion cells were more heavily impregnated than the fibers arising in the sympathetic trunk ganglia. He could trace axons of the cardiac ganglion cells to their terminations in the atrial and auricular musculature and the nodes of the conductive system but not into the ventricular musculature. The less heavily impregnated sympathetic fibers could be traced into the ventricular musculature as well as into the atrial and auricular muscle and the conductive system.

The anatomical data set forth above corroborate the results of the experimental studies of Cullis and Tribe (1913) who found that after section of the atrio-ventricular bundle in rabbits, vagus stimulation was without effect on the ventricles. On the basis of this result and the effect of atropine and pilocarpine, they concluded that the vagi supply no fibers to the ventricles and that the influence of vagus stimulation on the ventricles in the intact heart is exerted through the atrio-ventricular bundle. On the basis of results obtained by sympathetic stimulation and the use of adrenin, they also advanced the opinion that the ventricles are abundantly supplied by sympathetic fibers. Wiggers and Katz (1920) also found, by the use of adrenin, that the cardiac accelerators exert a direct influence on the ventricular musculature. On the basis of clinical studies DeGraff and Weiss (1925) concluded that the sympathetic cardiac nerves exercise considerable control over the ventricles in complete heart block, whereas the vagi exert only a slight influence. On the other hand, the vagus control of the atria in complete heart block is essentially the same as in the normal heart.

As the fibers which supply the cardiac muscle approach their termina-

tions, they form delicate plexuses around the muscle fibers According to Woollard (1926), the nerve fibers composing these plexuses ultimately penetrate the individual muscle cells and running in the sarcoplasm sometimes extend through the protoplasmic bridges into adjacent muscle fibers, giving off occasional terminal twigs which end in small bulb-like enlargements or loops Jones (1927) also described intracellular terminal structures in the ventricular muscle of the cat According to Boeke (1933), nerve fiber terminations of this character, which usually lie in proximity to the nucleus of the muscle cell, occur only in relatively small numbers in the myocardium He emphasized the importance of the terminal plexus in the cardiac muscle previously described by Fukutake (1925), which he regards as comparable to the terminal plexus in smooth muscle, through which the autonomic fibers effect functional connections with the muscle cells In intra vitam methylene blue preparations of the rat's heart, King (1939) observed no plexuses around the muscle fibers but described terminal structures of efferent fibers both on the surface of the muscle cell and within the sarcoplasm A single nerve fiber may supply terminal branches to more than one cardiac muscle cell A single muscle cell also may be innervated through more than one efferent nerve fiber

Afferent—The afferent innervation of the heart received little attention from the earlier investigators Berkley (1894) suggested that certain terminal structures which he observed, which could not be interpreted as motor endings, might be receptors Smirnow (1895), Dogiel (1898) and Michailow (1908) described terminal structures, particularly in the subendocardial tissue, which may be regarded as afferent nerve endings Woollard (1926) described similar structures in the epicardium which underwent degeneration following section of the vagi These he concluded represent receptors associated with afferent components of the vagus nerves

In methylene blue preparations of the cat's heart, Nettleship (1936) described an endocardial plexus made up of fibers and small nerve trunks which are continuous with the network of nerves beneath the epicardium It is present throughout the atria and ventricles and extends onto the atrio-ventricular and semilunar valves It is most highly developed over the inferior portion of the interatrial septum The fibers in this plexus are unmyelinated or thinly myelinated but derived from heavily myelinated fibers Its afferent nature is demonstrated by the observation that it undergoes extensive degeneration following section of the vagus nerves distal to the nodose ganglion but not following section of these nerves proximal to the nodose Ablation of the spinal ganglia in the upper thoracic segments resulted in no extensive degeneration of the endocardial plexus except near the apices of the ventricles

Well defined terminal structures associated with the endocardial plexus are relatively rare The simplest ones, as described by Nettleship, are uncomplicated twigs which terminate in dot-like expansions which may be single or double The more complex fiber terminations involve more or less elaborate arborization of the terminal branches These terminal structures probably do not represent the only receptive areas Not infrequently nerve fibers within the plexus split, interweave coil and twist upon themselves forming structures which Nettleship has designated "sensory nodal points"

In methylene blue preparations of the rat's heart, King (1939) described encapsulated nerve endings in the wall of the ventricle lying between bundles of muscle fibers, muscle spindles of varying complexity, and simpler configurations of terminal branches on the surface of muscle fibers. These structures are all regarded as receptors since they are connected with relatively large myelinated nerve fibers.

Nettleship (1936) also described a plexiform structure surrounding the basal portions of both the aorta and the pulmonary artery which in part lies adjacent to the adventitia of these great vessels. It is derived from the subepicardial network at the base of the heart but is quite distinct from the endocardial plexus. This plexus underwent extensive degeneration following section of the vagus nerves distal to the nodose ganglia but not following section proximal to these ganglia, extirpation of the stellate ganglia or ablation of the spinal ganglia in the upper thoracic segments, consequently, it must be regarded as made up mainly of the terminal branches of afferent vagus fibers.

Innervation of the Coronary Arteries — The coronary arteries exhibit a very abundant nerve supply. Large fibers of vagus origin terminate in the adventitia apparently without penetrating the media. These undoubtedly are afferent. The media is richly supplied, mainly through unmyelinated fibers of small caliber. Most of these probably are sympathetic but fibers which arise in the cardiac ganglia also may be traced directly to the coronary arteries (Woollard, 1926). This abundant nerve supply also extends along the branches of the coronary arteries as far as the arterioles.

Following extirpation of both stellate ganglia Woollard found that a large percentage of the nerve fibers in the media of the coronary arteries and their larger branches underwent degeneration but the supply to the smaller branches and arterioles was affected to a lesser degree. He, therefore, concluded that the coronary arteries are supplied with both sympathetic and parasympathetic nerves but the smaller branches and arterioles are innervated mainly through parasympathetic nerves. This finding is corroborated by experimental data reported by Nettleship (1936). In his experiments, bilateral extirpation of the stellate ganglion in the cat resulted in degeneration of one-half to three-fourths of the plexus on the coronary arteries but the finer nerve fibers supplying the coronaries and the plexuses on the arterioles and capillaries remained intact. These findings are of particular interest in view of the widely divergent results of physiological studies involving coronary vasodilatation and vasoconstriction.

In Nettleship's experiments, ablation of the spinal ganglia in the upper thoracic segments resulted in degeneration of some of the larger fibers in the coronary plexuses indicating their afferent character. Section of the vagi distal to the nodose ganglia, on the other hand, resulted in but little degeneration in the coronary plexuses. These results indicate that the major portion of the afferent innervation of the coronary vessels is effected through spinal nerve components.

Functional Relationships of the Cardiac Nerves —Intrinsic Nerves —The intrinsic cardiac nervous system obviously mediates the regulatory control which is exercised through the visceral components of the cerebrospinal nerves involved in the innervation of the heart but to what extent the various activities of the heart depend on impulses emanating from the central nervous system is not fully known. Rhythmic contraction of the

heart is not dependent on the central nervous system but this does not necessarily imply that rhythmic cardiac contraction may go on independently of the intrinsic cardiac nerves, although the capacity for rhythmic contraction is inherent in cardiac muscle

Various investigators have maintained that the cardiac plexus includes a system of local reflex mechanisms Morphological evidence for the existence of intracardiac reflex arcs must be regarded as inconclusive The fact that rhythmic contractions of the heart may continue after its connections with the central nervous system are severed, or even after it is removed from the body, does not warrant the assumption of an intrinsic reflex mechanism It only shows that the isolated heart possesses automaticity, *i e*, the heart with its intrinsic nerves possesses the capacity to initiate and carry out the various phases of cardiac activity in the proper sequence to bring about coordinated contractions of its various parts

The normal sequence of contraction of the cardiac musculature probably involves differentiated conduction systems and graded differences in the degree of responsiveness to stimulation These conduction systems are not nervous in the ordinary sense The cycle of contraction is initiated in the region adjacent to the entrance of the superior vena cava into the right atrium, *i e*, the area which corresponds to the sinus venosus in the more primitive vertebrate heart This area in which the contraction phase also continues longest, may be regarded as the seat of the pacemakers for the entire heart

If the sinus is the seat of the pacemakers of the heart beat, *i e*, if it dominates the rhythmic contractions of the entire heart as the best evidence available seems to indicate, how are the impulses which arise in this area transmitted to the rest of the heart? A discussion of the physiological data bearing on this point is not within the scope of the present volume The available evidence favors the view that, at least in the cold-blooded heart, the propagation of the beat is myogenic

Conclusions drawn from the results of experimentation on the hearts of cold blooded vertebrates cannot be accepted as valid for warm-blooded vertebrates without first establishing the structural relationships between cold-blooded and warm-blooded hearts In all vertebrate embryos the heart arises as the so called cardiac tube The remains of this primitive tube are not apparent in the mammalian heart on superficial examination but it has been shown by careful anatomical studies that it exists *in* the mammalian heart in the specialized tissue which makes up the atrioventricular bundle This tissue is histologically distinct from the rest of the cardiac tissue and is disposed in a manner which suggests that it is the main pathway along which the heart beat is propagated

At the upper end of this bundle, in the mammalian heart, is the atrioventricular node This structure, situated near the posterior margin of the interatrial septum, consists of an aggregate of peculiar primitive cells and fibers It is continued downward to the interventricular septum At a point a little in front of the attachment of the septal valve it bifurcates into right and left branches which continue toward the apex of the heart just beneath the endocardium on each side of the interventricular septum Each branch ultimately gives rise to an intricate system of smaller branches which become reflected over the inner surfaces of the ventricles These

branches are made up of the so-called Purkinje fibers which ultimately terminate in close relationship with the papillary muscles

As stated above, the cycle of contraction is initiated in the region at the mouths of the venae cavae. The evidence available strongly favors the conclusion that the heart beat actually originates in the sinu-atrial node. From this point it probably spreads through the muscular tissue of the atrial wall until it reaches the atrio-ventricular node. It is then transmitted to the ventricles along the atrio-ventricular bundle. This fact has been most clearly demonstrated by experiments involving heart-block. If, in the mammalian heart, a clamp is so arranged that it compresses practically nothing but the atrio-ventricular bundle, partial or complete heart block may be produced at will. When moderate pressure is applied, ventricular contraction follows regularly every second, third or fourth atrial contraction. When the pressure is extreme, the rhythm of the ventricle becomes entirely independent of that of the atrium. When the pressure is relieved the heart-block usually disappears and the normal sequence of atrial and ventricular contractions is reëstablished.

From the atrio-ventricular bundle, the impulse is propagated along its many branches which terminate in close association with the papillary muscles. *These muscles are the first part of the ventricular musculature to contract.* This obviously is significant in connection with the function of the papillary muscles in putting the chordæ tendineæ under tension, so as to keep the atrio-ventricular flaps from bulging into the atria when at the beginning of ventricular contraction high intraventricular pressure is brought to bear on their ventricular surfaces. After being initiated at these points in the ventricle, the wave of contraction seems to spread through the muscle at a fairly uniform rate.

The atrio-ventricular bundle is abundantly supplied with both sympathetic and parasympathetic nerve fibers. Conduction through the atrio-ventricular bundle is known to be subject to alteration by impulses reaching it through the cardiac branches of the vagi, particularly those of the left vagus. Experimental data reported by Puddu (1937) support the assumption that vagus stimulation does not exert a direct effect on the cardiac musculature but results in the liberation of an acetylcholine-like substance in the sinus area, the effect of which is transmitted to the musculature through the atrio-ventricular bundle.

Extrinsic Nerves.—The control exercised through the extrinsic innervation of the heart on cardiac activities is primarily regulatory. In general cardiac inhibition is mediated through the vagi and cardiac acceleration through the sympathetic cardiac nerves. The extrinsic cardiac nerves also mediate impulses which modify the force of the heart beats and the conductivity of the cardiac muscle.

The effect on the heart of vagus stimulation, under normal physiological conditions, is inhibitory, but cardiac acceleration due to impulses conducted by the vagi has been demonstrated experimentally. Brouha and Nowak (1939) reported cardiac acceleration in dogs following the administration of atropine twenty days or longer after total sympathectomy. Brouha, Nowak and Dill (1939) reported cardiac acceleration in totally sympathectomized dogs due to muscular exercise and emotional excitation. These results could be consistently abolished by intracranial bilateral vagus section. Cardiac acceleration due to muscular exercise in totally

sympathectomized dogs could be recognized fourteen days after the operation, but did not reach its maximum until approximately one year after operation. The cardiac acceleration observed in these totally sympathectomized animals obviously represents a shift of function to potential mechanisms which normally are not brought into play. This shift requires a certain length of time. The sensitivity of the mechanisms involved apparently develops gradually after the normal accelerator mechanisms are destroyed.

Kabat (1940) demonstrated the existence of cardio accelerator fibers in the vagus nerves of the dog by electrical stimulation of the vagus rootlets intracranially. They are present predominantly in the right vagus. They cannot be excited reflexly by stimulation of the carotid sinus or afferent vagus fibers but respond promptly to acute cerebral anemia. The chemical mediator liberated at the terminations of these fibers in the heart probably is sympathin. Their threshold of stimulation is somewhat higher than that of the cardio inhibitory fibers. They probably play no significant rôle in cardiac control under normal physiological conditions.

The results of physiological studies (Cohn, 1912, Robinson, 1913, Cohn and Lewis, 1913, Fogelson, 1929) have shown that in mammals the right vagus acts mainly on the sinu-atrial node and the left vagus on the atrio-ventricular bundle. This is also in agreement with the results of experiments carried out on cold blooded animals. Stimulation of the right vagus always results in retardation and weakening of both the atrial and the ventricular beats. Stimulation of the left vagus sometimes has little influence on the atrial beat, although it may bring about a condition of partial heart-block. If the atrio-ventricular bundle is clamped so that a condition of partial heart block already exists, stimulation of the left vagus may result in complete heart-block. The left vagus also exerts a direct influence on the ventricles which affects the force of contraction rather than the rate.

The results of experimental studies carried out on the dog's heart by Bachmann (1923) indicate quite clearly that the various ganglion cell groups associated with the sinu-atrial junction are related to both vagi. Average computations based on the effects of the administration of nicotine and destruction of various parts of the area involved by a coagulating fluid show that the left vagus is distributed predominantly to the superior caval ganglia and the ganglia at the head of the sinu atrial node, and the right vagus to the intercaval ganglia and those at the tail of the sinu-atrial node. In most cases the ganglia in the coronary sinus receive only fibers of the left vagus. On the basis of these findings, it may be assumed that the greater inhibitory power of the right vagus noted above is directly related to its more extensive distribution to the ganglia associated with the sinu-atrial node. The quantitative distribution of both vagus nerves to the ganglia associated with the sinu-atrial node, as pointed out by Bachmann, varies widely in different animals, the average order of dominance being sometimes reversed in individual cases.

According to Fogelson (1929), stimulation of the sympathetic cardiac nerves on the right side results in greater acceleration of the cardiac rhythm than equal stimulation of the sympathetic cardiac nerves on the left side. Stimulation of the right sympathetic cardiac nerves also augments the force of the atrial contraction, but has no marked effect on the

force of the ventricular contraction It exerts no effect on the interval between atrial and ventricular contractions Stimulation of the left sympathetic cardiac nerves, on the contrary, exerts no marked influence on atrial contraction but augments the force of ventricular contraction It also tends to shorten the interval between atrial and ventricular contractions Section of the sympathetic cardiac nerves results in no marked depression of the basal heart rate In experiments reported by Murphy (1942), the near basal heart rate of normal unapprehensive dogs which had been without food for twelve hours and had rested quietly for one hour showed a range of 50 to 56 beats per minute This rate was not appreciably changed following bilateral extirpation of the upper five thoracic segments of the sympathetic trunk, including the stellate ganglion

Afferent impulses coming from any part of the body may influence the heart through the vagi Stimulation of the central end of any sensory nerve in mammals usually results in retardation of the heart beat but some times elicits cardiac acceleration Certain afferent nerves are more sensitive in this respect than others Stimulation of the pulmonary branches of the vagi usually results in marked cardiac inhibition Stimulation of trigeminal fibers through the mucosa of the upper respiratory passages, as by inhalation of irritating vapors likewise brings about strong cardiac inhibition Profound cardiac inhibition also is elicited by violent stimulation of the mesentery, as by a blow on the abdomen, or by irritation of the sensory nerves of the gastro intestinal canal either mechanically or by disease

In experiments reported by Pearcy and Howard (1927), distention of a segment of the intestine by means of a balloon, in a narcotized dog in which the heart was poisoned by barium chloride or digitalis elicited cardiac reflexes which resulted in an elevation of the T-wave and a decrease in the R to end of T-interval These reflexes were not abolished by section of the vagi They advanced the opinion that distention of the intestine may react upon the heart in a similar manner in the presence of any disease which damages this organ In anesthetized dogs in which the heart had not been poisoned, as reported by Owen (1933), distention sudden collapse or irritation of the hollow viscera rarely elicited cardiac arrhythmias In dogs which had been jaundiced by reason of obstruction of the flow of bile, distention of the bile duct caused either ectopic atrial beats or heart-block which usually was associated in time of occurrence with the appearance of retching or vomiting Crittenden and Ivy (1933) also reported that nausea, retching and vomiting produced by the subcutaneous injection of apomorphine in dogs may elicit cardiac irregularities, such as heart-blocks, cardiac arrests and atrial or ventricular ectopic beats In their experiments nausea usually was accompanied by tachycardia, and retching by bradycardia

Retardation of the heart-rate in man may be caused by direct stimulation of the vagus center, as by the pressure of a blood clot or tumor in the medulla, or by the reaction of this center to some unusual hormone in the blood In experimental animals, according to Reid (1931), metabolites from an ischemic limb passing into the blood result in retardation of the cardiac rhythm The vagus center also is stimulated by a general increase in intracranial pressure In the experiments of Anrep and Starling (1925) and Anrep and Segall (1926) a rise in general cerebral pressure caused

slowing of the heart-rate Various other conditions which result in direct stimulation of the vagus center, likewise, cause temporary or prolonged retardation of the cardiac rate

An increase in the blood pressure in the carotid arteries, under normal conditions, results in retardation of the heart-rate External pressure in the vicinity of the bifurcation of the common carotid artery likewise may elicit reflex bradycardia In seeking an explanation of these reflexes Hering (1923) found that they have their origin in the dilated proximal portion of the internal carotid artery, now commonly known as the carotid sinus In a series of later studies (1924–1930) he verified and extended his earlier findings regarding these reflexes Other investigators, notably de Castro (1926, 1928), Heymans (1929) and Sunder-Plassmann (1930) corroborated Hering's findings regarding the origin of these reflexes and demonstrated both anatomically and experimentally that the nerve fibers which constitute the afferent limbs of the reflex arcs employed are afferent components of the glossopharyngeal nerves The inhibitory impulses are conducted to the heart by visceral efferent components of the vagi The reflex connections undoubtedly are effected in the nucleus of the vagus nerve

Cardiac acceleration is mediated through the sympathetic cardiac nerves, but does not involve the entire sympathetic supply Hering (1924) could not elicit cardiac acceleration by stimulation of the cervical sympathetic trunk in mammals (dog, cat, rabbit, ape) Sluif and Bruning (1926) also failed to elicit acceleration of the heart-rate in man by stimulation of the superior and middle cervical sympathetic cardiac nerves On the other hand, stimulation of the roots or communicating rami of the upper thoracic nerves, particularly those of the second and third, or the post-ganglionic fibers running from the stellate and upper four or five thoracic sympathetic ganglia to the heart always results in cardiac acceleration The accelerator fibers probably are conveyed to the heart mainly in the inferior cervical and thoracic cardiac nerves In addition to bringing about cardiac acceleration, sympathetic stimulation also modifies the conductivity and contractile power of the cardiac musculature

Sympathetic stimulation differs from vagus stimulation of the heart in that a longer latent period elapses before it becomes effective The effect of sympathetic stimulation also continues longer than that of vagus stimulation after the stimulus is withdrawn When the vagus and sympathetic nerves are stimulated simultaneously the vagus effect consequently, is observed first and is usually followed, after the removal of the stimulus, by the sympathetic effect If stimulation of both nerves is continued for a long time, the vagus becomes fatigued and permits the sympathetic to become effective earlier than it would if the vagus alone were stimulated The sympathetic influence, however is never as strong as the vagus influence Vagus and sympathetic nerves therefore, are not antagonistic in the sense that the influence of the one is neutralized by that of the other but when both are stimulated simultaneously the heart responds first to the vagus and later to the sympathetic This difference in the response of the heart to vagus and sympathetic stimulation probably is an important factor in the normal functioning of the organ It also lends support to the theory that the vagus center is dominant in the regulatory control of the heart which is mediated through its extrinsic nerves

Acceleration of the heart-rate may be brought about either by diminution of impulses from the vagus center or by increase in impulses from the spinal accelerator centers Reflexes carried out through the spinal centers which influence the heart-rate, may be demonstrated under experimental conditions If both vagi are cut and the peripheral end of one of them is stimulated sufficiently to keep the heart beating at almost its normal rate stimulation of certain sensory nerves may elicit acceleration of the heart beat Under normal conditions reflex control of cardiac rhythm through the spinal accelerator centers probably is much less important than reflex control through the vagus center

A rise in body temperature or application of heat to the skin elicits reflex cardiac acceleration through the spinal accelerator centers Reflexes initiated in the cutaneous thermal receptors probably are more significa in the regulation of cardiac rhythm than changes in body temperatur Accelerator reflexes are initiated more readily by a hot water bath than b dry air radiant heat applied to the skin (Benson, 1938) Muscular activity may elicit reflex cardiac acceleration even though the general body temperature is not increased This reaction, according to Alam and Smirk (1938) is due to the stimulating effect of metabolites which accumulate in the active skeletal muscles

Afferent impulses arising in the heart and proximal portion of the aorta reach the central nervous system via both the vagus and sympathetic nerves The afferent impulses conducted from the heart and aorta through the vagi probably do not reach the threshold of consciousness, but elicit reflex vasomotor responses In experiments reported by Spiegel and Wassermann (1926) stimulation of the vagi by distention of a portion of the aorta isolated by a ligature at either end gave rise to no pain reactions The results of experiments reported by White Garrey and Atkins (1933) also indicate that impulses of cardiac origin conducted by the vagi do not give rise to pain Impulses of cardiac origin which eventuate in pain according to their findings are conducted into the central nervous system solely by afferent fibers associated with the sympathetic cardiac nerves

The so-called depressor nerve plays an important role in the regulatory control of the heart through its influence on both the cardio-inhibitory and vasomotor centers Whenever the blood pressure rises above its normal limits the depressor fibers are stimulated probably by the mechanical effect of the increased intracardiac pressure, and conduct impulses to the medulla which tend to bring about reflex inhibition of the heart through the vagus center and inhibition of vascular tonus through the vasoconstrictor center

In addition to the depressor fibers the vagus nerves include some cardiopressor fibers at least in some cases McDowall (1935) demonstrated such fibers in approximately half the cats used in his experiments

The heart is protected against variations in arterial pressure and bloo supply not only by depressor reflexes initiated in the cardio-aortic press receptive zone but also through other pressoreceptive reflex mechanisms The coronary blood flow depends in part on the pressure in the aorta The pressures in the aorta the left atrium and the left ventricle depend mainly on the pressoreceptive sensitivity of the left ventricle, the aortic arch and the pulmonary artery The venous pressure and the pressure in the pulmonary artery and consequently, the pressure in the right atrium and

ventricle are regulated at least in part by the pressoreceptive sensitivity of the pulmonary arteries and veins, the venae cavae and the right atrium (Heymans, 1938).

Chemoreceptive reflexes play a significant role particularly in the regulation of the cardiac output. When the human subject, on a tilting board, is tilted passively to the upright position the pulse rate is increased and the cardiac output diminished. These changes are correlated with the shift of blood from the trunk to the lower extremities (Asmussen, Christensen and Nielsen 1939). Cutaneous vasoconstriction also is indicated by a reduction in skin temperature. The cardiac acceleration and the vasoconstrictions which occur on tilting undoubtedly are reflex responses to stimulation of the pressoreceptors in the cardio-aortic pressoreceptive zone and the carotid sinus which tend to maintain the blood pressure at normal levels, but do not tend to increase the cardiac output. Asmussen and Knudsen (1942) have found that if the subject on the tilting board whose cardiac output is decreased, breathes air low in O_2, the volume of the blood issuing from the heart is increased, which indicates that stimulation of the chemosensitive receptors initiate reflexes which tend to increase the cardiac output. Similar reflexes also are initiated by the onset of work.

The literature bearing on the regulation of the coronary circulation is voluminous and records many conflicting observations. In a comprehensive review of this literature Anrep (1926) pointed out that the weight of evidence favors the hypothesis that constriction of these vessels is mediated through the parasympathetic nerves, their dilatation through the sympathetic nerves. The results of certain later studies, particularly those of Greene (1939, 1934) Danielopolu and Margou (1933), Gollwitzer-Meier and Kruger (1935) and Bartschi (1936) support this assumption, while those of others support the opposite point of view. In experiments reported by Kountz Pearson and Koenig (1934), vagus stimulation resulted in retarding the rate of contraction of the normal human heart and increasing the flow of blood through the coronary vessels, sympathetic stimulation resulted in accelerating the heart rate and reducing the coronary flow. In perfusion experiments on the revived human heart, vagus stimulation reduced the coronary flow and sympathetic stimulation increased it while there was dissociation of atrial and ventricular contractions and the rate of contraction was not influenced by nerve impulses. The action of drugs which in the beating heart, increase muscular activity and decrease coronary flow simulated the effects of sympathetic stimulation, that of drugs which cause dilatation of the beating heart and increased coronary flow simulated the effects of vagus stimulation. No comparable similarity was noted between effects of nerve stimulation and the action of drugs which exert their influence primarily through the constrictor and dilator fibers to the coronary vessels. On the basis of these experimental results the conclusion was advanced that in man the cardiac nerves exert their influence on the coronary flow mainly through changes in the state of the cardiac muscle. The results of experiments carried out on the dog's heart in a state of ventricular fibrillation reported by Katz and Jochim (1939) seem to support the assumption that the vagi include only cholinergic coronary vasodilator fibers which are tonically active while the sympathetic cardiac nerves include both adrenergic coronary vasodilator and adrenergic coronary vasoconstrictor fibers which are tonically active, the

action of the sympathetic nerves being predominantly vasoconstriction. These experimental results, like those of Kountz *et al.* seem to be valid but in view of the volume of the data which have been interpreted as supporting the assumption that constriction of the coronary vessels is mediated through the parasympathetic nerves and their dilatation through the sympathetic nerves, this problem cannot be regarded as finally solved.

In a study of the effect of the activity of skeletal muscles on the coronary circulation, Greene (1941) found that the coronary flow is sharply augmented at the beginning of muscular activity and the coronary dilatation persists into the after period. He advanced the opinion that reflex coronary dilatation associated with muscular activity is a major factor in the nutrition of the heart during the added strain incident to the activity of skeletal muscles. In experiments reported by Essex, Herrick, Baldes and Mann (1943), the effects of exercise on coronary flow did not differ essentially in dogs which had been subjected to sympathetic denervation of the heart and normal control animals. In the absence of marked cardiac acceleration and elevation of blood pressure the coronary flow was not modified by exercise. In animals with vagotomized or totally denervated hearts the coronary flow appeared to be influenced mainly by the blood pressure.

CHAPTER VIII

INNERVATION OF THE BLOOD VESSELS

Anatomic Data.—Source of the Nerve Supply.—The innervation of the blood vessels includes both efferent and afferent nerve fibers. The efferent fibers include both vasoconstrictors and vasodilators. The former are mainly sympathetic, the latter include both sympathetic and parasympathetic components. The afferent fibers distributed to the blood vessels are components of the sensory cerebrospinal nerve roots. Certain vascular areas, particularly (1) the proximal portion of the aorta including the aortic arch and the aortic bodies, the proximal portion of the pulmonary artery and the cardiac walls adjacent to the great vessels, and (2) the carotid sinuses and carotid bodies are supplied with special afferent nerves. Those which supply the former area, which may be called the cardio-aortic zone, are branches of the vagi which are called the depressor nerves. The carotid sinuses and carotid bodies are supplied through branches of the glossopharyngeal nerves known as the carotid sinus nerves (Fig. 40). The carotid sinus may also receive an afferent branch of the vagus. These vascular areas, with their afferent nerves, may be regarded as presso-receptive and chemoreceptive mechanisms.

The large blood vessels of the trunk, *e. g.*, the aorta and inferior vena cava, are supplied quite directly by the autonomic nerves nearest to them. In the thorax, these vessels receive fibers directly from the sympathetic trunks and the cardiac plexus. In the abdomen they are supplied by rami from the plexuses along the aorta. The arteries and veins supplying the abdominal organs in the main are innervated in the same manner. The vessels in the neck and head derive their efferent innervation mainly from the cervical sympathetic ganglia. Rami from the inferior cervical and upper thoracic ganglia form a plexus on the vertebral artery which extends cephalad. This plexus, according to Rynders (1933), also receives fibers through the gray communicating rami of all the cervical nerves. Rami from the superior cervical ganglion form a rich plexus on the internal carotid and a lesser plexus on the external carotid artery through which the sympathetic system is extended into the head. Rami from the inferior cervical and upper thoracic sympathetic trunk ganglia also join the common carotid artery, giving rise to a plexus on this artery which is continuous with those on the internal and external carotid arteries. The peripheral vessels are supplied by sympathetic fibers which join them via the somatic nerves which lie in closest proximity to them. Afferent nerve fibers in general reach the blood vessels via the nerves through which they receive efferent fibers.

The older anatomists were conversant with the anatomical fact that the peripheral vessels are joined by nerves along their courses. Goering (1836) and Frey (1874–1876) stated very definitely that the peripheral arteries and veins are innervated through branches of the nerves which lie closest to them. According to Kramer and Todd (1914) the subclavian and axillary arteries receive their nerve supply directly from the sympathetic

trunk, but all the more distal arteries in the upper extremity are supplied with sympathetic fibers which are conveyed peripheralward in the spinal nerves and distributed to the various blood vessels at irregular intervals. The vessels in the more distal parts of the limbs, particularly those in the hands, are joined by branches of the adjacent nerves at more frequent intervals than those in the proximal parts of the limbs.

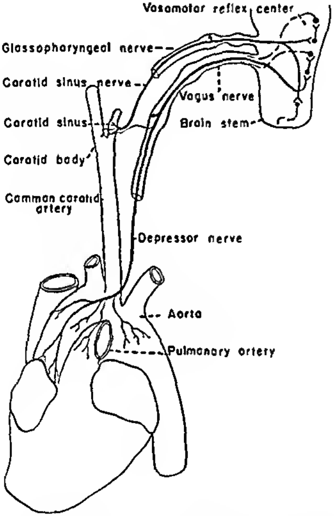


FIG. 40.—Diagrammatic illustration of the depressor and carotid sinus nerves.

The plexus on the abdominal aorta gives rise to a subordinate plexus on the common iliac artery, from which some fibers extend to the proximal portion of the femoral artery, but the more distal portions of the femoral artery and the other vessels of the lower extremity, like those of the upper extremity, are supplied with sympathetic fibers which are conveyed peripheralward in the somatic nerves and are distributed to the vessels at irregular intervals (Potts, 1915). The distribution of nerves to the large arteries of the lower extremity, as observed in a careful dissection, is illustrated in Figure 41.

In a critical study of the extrinsic innervation of the vessels of the extremities, Hirsch (1925) employed minute dissection under moderate magnification following silver impregnation of the nerves. The results

of this study do not support the theory that long fibers derived from the aortic plexus accompany the peripheral arteries in any considerable num-

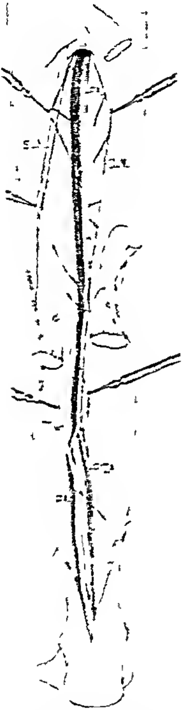


FIG. 41

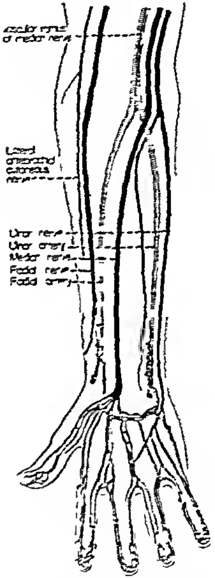


FIG. 42

FIG. 41.—Drawing from a dissection of the lower extremity showing the distribution of nerves to the large arteries. F.A., Femoral artery; Ob.N., obturator nerve; P.A., popliteal artery; P.T.A., posterior tibial artery; Sc.N., sciatic nerve; T.N., tibial nerve. (Dissection by Mr. I. Levy.)

FIG. 42.—Drawing from a dissection of the upper extremity showing the distribution of nerves to the arteries of forearm and hand.

bers but show clearly that the peripheral vessels are supplied by rami from the adjacent nerves at intervals all along their courses. He regularly

found but few fibers extending along the common iliac artery from the aortic plexus. Only a minor portion of these become definitely related to the artery. As soon as the genito-femoral nerve comes into close proximity to the external iliac artery, it supplies branches to the latter. The femoral artery is supplied mainly by branches of the femoral and saphenous nerves. Fiber bundles extending along the external iliac artery from the plexus on the common iliac could not be demonstrated. Hirsch properly maintained that if long fibers extending along the course of the artery were present in sufficient numbers to play an appreciable role in the innervation of the femoral artery and its widely distributed branches, there would be no difficulty by the method employed in detecting their presence.

The subclavian and the proximal part of the axillary artery are commonly supplied by fibers derived directly from the sympathetic trunk. According to Hirsch, the axillary and the proximal part of the brachial artery also receive fibers from the brachial plexus. Farther distalward the brachial artery is supplied by branches of the several nerves which lie in proximity to it. In the upper part of the arm it is supplied mainly by branches of the radial and cutaneous nerves of the forearm. The distal half of the brachial artery is supplied mainly by branches of the median nerve. The musculocutaneous nerve does not regularly supply branches to the brachial artery. The ulnar nerve occasionally supplies a few branches to its middle and distal parts.

These findings of Hirsch, which in their main aspects have been corroborated by many anatomical, physiological and clinical observations, show clearly that the number of branches joining the vessels of the extremities from adjacent nerves is far greater and the total extrinsic nerve supply of these vessels is far richer than has been generally assumed. Many of the smaller nerves which join these vessels are so delicate that they cannot be detected by the ordinary methods of dissection. These finer rami are regularly imbedded in connective tissue. In general, they run nearly parallel with one another from the nerve trunk to the vessel but not infrequently they exhibit more or less complex intercommunications with one another. As they enter the adventitial plexus, some of their fibers become immediately incorporated in the adventitia, while others pass through the adventitia quite directly and enter the media or, passing through only the superficial layers of the adventitia ramify in its deeper layers.

According to Woollard and Phillips (1933), the peripheral vasomotor and other sympathetic fibers have the same distribution as the nerves which convey them peripheralward, *e. g.*, the sympathetic fibers in the median or ulnar nerves are limited to the areas supplied by the somatic components of these nerves respectively, and the lines of demarcation are as sharply drawn as those of the cutaneous nerves. Telford and Stopford (1933) have concurred in this conclusion with respect to the constrictors of the cutaneous vessels but not with respect to dilators of these vessels and both constrictors and dilators of the deep vessels. They have pointed out that the profound vasodilatation succeeding irritative lesions of such nerves as the median and ulnar is not confined to the cutaneous territory of the affected nerve. They also have advanced certain evidence in support of the view that the innervation of the deep vessels of the palm is less simple than that of the cutaneous vessels. The rami which join the per-

ipheral vessels include both myelinated and unmyelinated nerve fibers The purely vascular rami include mainly postganglionic and afferent fibers The distribution of nerves to the arteries of the forearm and hand is illustrated in Figure 42

According to Woollard's findings in normal animals (rat, guinea pig cat, dog), bundles of nerve fibers extend from the plexus on the aorta along the iliac artery, forming an interlacing plexus As these bundles are traced distalward along the femoral artery, they gradually become smaller and disappear somewhere in the distal part of the femoral region The femoral artery is joined by twigs from the adjacent nerves, the majority of which are very small They are composed on the average of five to ten fibers These twigs become more numerous as the arteries grow smaller The arterioles, according to Woollard, "are enmeshed in the ramifications of the nerve bundles"

The proximal portion of the vascular tree in the extremity, according to Burns (1935), is supplied with fewer sympathetic nerve fibers than the more distal portions He found no nerve bundles coursing for more than a half inch along a vessel or within its wall in the hind limb of the cat The nerve fibers commonly enter the vessel wall in bundles which penetrate the adventitia and join the plexus at the border of the adventitia and media

The blood vessels in the vertebral canal, including the intramedullary vessels of the spinal cord are supplied with sympathetic nerve fibers segmentally from the sympathetic trunks through rami which traverse the intervertebral foramina These rami also include afferent components of the corresponding spinal nerves

The intracranial vessels, including the dural sinuses are supplied with sympathetic nerve fibers mainly via the plexuses on the vertebral and internal carotid arteries According to Chorobski and Penfield (1932), some of the preganglionic fibers involved in the sympathetic innervation of these vessels terminate in relation to ganglion cells located at levels higher than the superior cervical ganglion An accessory sympathetic ganglion not infrequently occurs on the internal carotid artery both in man and lower mammals In some cases sympathetic ganglion cells also occur scattered along the internal carotid According to their findings the intracranial vessels also have a parasympathetic innervation the postganglionic fibers of which are derived mainly from ganglion cells located in proximity to the anastomosis of the greater superficial petrosal with the internal carotid nerve The preganglionic fibers which end in relation to these ganglion cells traverse the greater superficial petrosal nerves Cranial nerve branches have been traced to the dura and dural vessels particularly from the trigeminal, glossopharyngeal, vagus and hypoglossal nerves Slender rami from most of the cranial nerves also join the pial and intracerebral vessels (McNaughton 1938) These cranial nerve branches undoubtedly include afferent fibers supplied to the vessel walls and the meninges Afferent components of the upper thoracic nerves enter the cerebral area via the plexuses on the common and internal carotid arteries (Kuntz 1934) Whether these fibers play a part in the innervation of intracranial vessels as yet is unknown

According to the older teaching, the intracerebral blood vessels are not subject to vasomotor control The results of more recent studies indicate an

abundant nerve supply to these vessels Stoehr (1922) and Dowgjallo (1932) described an abundant nerve supply to the pial vessels Clarke (1929) demonstrated perivascular nerves within the medullary substance in the spinal cord and the medulla oblongata in cats and dogs Kurusu and Hamada (1929) described nerves in the adventitia and media of small intracerebral arteries in dogs and monkeys Grigorjewa (1932) also reported intracerebral vascular nerves in certain mammals Penfield (1932) demonstrated unmyelinated nerve fibers associated with intramedullary vessels throughout the central nervous system in various mammals, including man These fibers were found to be continuous with the nerves associated with the pial vessels and could be traced onto arterioles as small as 20 to 30 microns in diameter (Chorobski and Penfield, 1932) The vessels of the choroid plexuses also have an abundant nerve supply which includes both efferent and afferent components (Stoehr, 1922, Clarke, 1928)

The chief pressoreceptive and chemoreceptive vascular areas are abundantly supplied with afferent fibers mainly of the vagus and glossopharyngeal nerves These areas include the proximal portions of the aorta and the pulmonary artery the terminal portions of the great veins and adjacent portions of the heart, the carotid sinuses and the carotid and aortic bodies The carotid and aortic bodies are not essential components of the vascular system but are intimately related to it both developmentally and functionally The carotid bodies also are developmentally related to the glossopharyngeal nerves, the aortic bodies to the vagi (Boyd, 1937)

The aortic (depressor) branches of the vagi as described by Nonidez (1935, 1937) particularly in the rabbit guinea pig and dog differ in their distribution on the two sides On the right side the aortic nerve terminates in relation to the innominate artery at the base of the right subclavian On the left side most of its fibers terminate in relation to the arch of the aorta and the pulmonary artery Both aortic nerves supply fibers to the aortic bodies adjacent to them The carotid sinus and the carotid body on either side receive their afferent innervation mainly through a ramus of the glossopharyngeal nerve, the carotid sinus nerve (Fig 40)

Distribution of Nerve Fibers in Vessel Walls—The intrinsic nerves of arteries and veins are arranged in a more or less definite manner Michailow (1908) described an outer plexus in the adventitia, a deeper plexus at the border between adventitia and media, and a deepest plexus in the media He designated them respectively the "adventitial" plexus, the "border" plexus and the "muscular" plexus Certain other investigators have not recognized a border plexus They also question the advisability of regarding the nervous complex in the media as a plexus (Hirsch, 1926) All concede that the adventitia and media are abundantly supplied with intrinsic nerve fibers but there is no general agreement regarding the existence of nerve fibers in the intima

According to Hirsch (1926), who studied the distribution and arrangement of the nervous elements in the walls of the larger vessels in the extremities in man the nerve fibers in the adventitia do not constitute a plexus at any given depth in this layer but occur in larger or smaller bundles throughout its entire thickness While in general, the nerve fibers run longitudinally in the adventitia, there is no reason to assume that individual fiber bundles continue along the vessel but short distances The fibers are in part myelinated and in part unmyelinated They enter

the adventitia through slender rami arising from the somatic nerves These rami can usually be traced but a short distance, if at all, along the vessel until they are lost in the adventitial tissue The fibers of any one ramus do not all take the same course in the adventitia Most of them seem to run distalward, but some run in the opposite direction Not uncommonly the fiber bundles are arranged with reference to the vasa vasorum, but to what extent they are functionally related to these small vessels is not apparent from the histological picture The vasa vasorum apparently afford convenient pathways for the nerve fiber bundles through the adventitial tissue In most instances, a fiber bundle which joins one of these small vessels accompanies it for a short distance and then deviates from its course through the connective tissue and joins another of the vasa vasorum Stohr (1922) described the same relationship of the nerves in the adventitia to the vasa vasorum in the blood vessels of the pia mater and chorioid plexus According to Hirsch, the capillaries in the adventitia commonly are accompanied by one or more nerve fibers but it is quite impossible, on the basis of histological observations, to decide whether these fibers are functionally related to the capillaries or merely accompany them through the connective tissue

Hirsch was not convinced, by the results of his studies, that the meshwork of nerve fibers in the adventitia should be regarded as a continuous plexus around the vessel, regardless of the abundance of its fibers Other investigators (Michailow, 1908, Glaser 1914, Woollard, 1928) have regarded it as a continuous plexus which completely encircles the vessel According to Woollard, this plexus occupies all planes of the adventitia, and exhibits essentially the same arrangement in both the larger and smaller vessels

Fiber bundles coursing through the adventitia enter the media Some of them seem to be derived from the plexiform meshwork in the adventitia, others enter the media quite directly from the rami through which the fibers are conveyed from the somatic nerves to the vessel These bundles include relatively fewer myelinated fibers and a larger proportion of unmyelinated ones of small caliber than those which ramify only in the adventitia (Kerper, 1927, Woollard, 1928) According to Michailow (1908), Dogiel (1910), and Glaser (1914), these nerves constitute a plexus in the muscularis which as described by Dogiel is made up of numerous varicose unmyelinated fibers and spreads out over the surface of the muscle layer as well as between the muscle fibers throughout the media Both Hirsch and Stohr observed a plexus on the surface of the circular muscle, but failed to find nerve fibers in the deeper layers of the musculature Burns (1935) described the nerve complex in the media as a network which exhibits true anastomoses Kerper (1927) observed unmyelinated fibers of small caliber throughout the entire musculature Woollard described the intramuscular plexus as a real nerve net composed of fibers which divide, rejoin, and divide again, forming a continuous fibrous structure throughout the length of the vessels Boeke (1932, 1933) has emphasized the abundance of nerve fibers in the arterial walls, particularly in the media According to his account the nerve fibers supplying the media form a dense intricate plexus which covers the entire muscular coat and extends between the muscle fibers so that it is present throughout the entire layer (Fig 43) The terminal elements of this plexus penetrate the muscle cells

and become continuous with an extremely delicate network within the cytoplasm Nonidez (1930) described nerve fibers in the superficial layers of the media, but denied the existence of a plexiform nervous structure throughout the media, as described by Boeke

Certain investigators, including Glaser (1924) and Okamura (1930), have maintained that nerve fibers also terminate in the intima Others particularly Hirsch, Stohr, Kerper, Burns and Nonidez have been unable to substantiate this claim

The intrinsic innervation of the veins has been studied less extensively than that of the arteries The data available suggest that the general plan of distribution of the nerve components observed in the arteries also obtains in the veins, with such differences as may be correlated with the relative ratio of muscle to the other tissue elements in the vessels

FIG 43 —Nerve plexus in the media of a small artery human parotid gland Bielchowsky method (Boeke Jour Comp Neur 1932 courtesy of the Wistar Institute)

Do Ganglion Cells Exist in the Vessel Walls?—Certain investigators, including Glaser (1924) and Okamura (1930) have reported the occurrence of ganglion cells in the walls of blood vessels Others observed ganglion cells in close proximity to blood vessels, but not within their walls, in various parts of the body, particularly the heart and the urinary bladder There is no reason to assume that such cells are functionally related to the vessel unless perchance they represent the peripheral components of visceral efferent chains which terminate in the vessel wall Their proximity to the vessel probably is purely circumstantial

Ganglion cells in the plexus on the internal carotid artery probably represent cells which were displaced from the superior cervical sympathetic ganglion during embryonic development and are comparable to the neurons in the latter ganglion There is no reason to assume that such cells become functionally related to the internal carotid artery unless they constitute the terminal links in visceral efferent chains supplying this artery The fact that such ganglia may become imbedded in the adventitial layer of the vessel wall does not necessarily indicate a functional relationship to the vessel

Small ganglia probably are normal constituents of the aortic plexus Like the major portion of this plexus they usually lie superficial to the aortic wall If any of them become imbedded in the adventitial layer of the aorta they probably are not differentiated functionally from the rest of the ganglia in the aortic plexus The only known functional relationship of autonomic ganglion cells to blood vessels is that of peripheral neurons in visceral efferent chains

Afferent Fiber Terminations and End Organs —Fiber terminations and end organs of considerable variety have been described in the adventitia, particularly in the larger arteries and veins Most of these probably are receptive organs which represent the terminal structures of myelinated afferent fibers They fall roughly into two classes (1) naked terminations consisting of terminal branches or terminal loops, and (2) encapsulated structures Naked terminations may consist of simple terminal branches which end in bulb-like enlargements, tree-like or brush-like endings, and very delicate loop-like structures which are sometimes relatively simple, and sometimes highly complex The tree-like and brush-like endings occur very commonly in the adventitia of the vessels of the extremities (Hirsch, 1926) and the coronary arteries (Woollard 1926) Encapsulated end organs in the adventitia are abundant and widely distributed Hirsch observed as many as fourteen such bodies in a single section They differ widely with respect to size and form, but exhibit the same general plan of architecture In general, they are composed of layers of spindle-shaped cells which are separated from one another by interlamellar layers of non-cellular substance In addition to the terminal loop of the nerve fiber, the interior of such a capsule contains a core of compact oval cells which, in silver preparations, usually appear darker than the surrounding tissue Some of these end organs conform to the usual description of Pacinian corpuscles Others resemble very closely the typical end bulbs of Krause Still others exhibit a structure which may be regarded as intermediate between these two extremes According to Hirsch the encapsulated end organs occur only in the outer layers of the adventitia Woollard (1928) emphasized the possible relationship to the blood vessels of certain encapsulated fiber terminations situated in the adjacent fatty tissue In some instances according to his findings, a medullated nerve fiber, which terminates in the adventitia by means of one branch, also terminates in a sensory end organ lying in the fatty tissue adjacent to the vessel by means of another branch Unencapsulated fiber terminations occur in all parts of the adventitia (Hirsch 1926)

The pressoreceptive and chemoreceptive vascular areas exhibit relatively elaborate terminal structures Sunder-Plassmann (1930) recognized afferent terminal structures of two general types in the adventitia of the carotid sinus both in man and animals According to his account, those of Type I are characterized by arborizations of relatively coarse structure, the branches of which end in coarse terminal nets (Fig 44) Those of Type II are characterized by more diffuse arborizations the branches of which are more slender and end in finer terminal nets (Fig 45) Terminal structures of both these types, according to Sunder-Plassmann, are limited to the adventitia Similar receptive end organs have been described in the proximal portion of the aorta by various investigators, including Katz and Saphir (1933), Nettleship (1936) and Seto (1937) Less elaborate receptive structures have been described in the proximal portion of the pulmonary artery and the carotid and aortic bodies (Nettleship 1936, Nonidez, 1935, 1937)

Nerve fiber terminations in the media have been described by relatively few investigators These are mainly the terminations of unmyelinated fibers in relation to the smooth muscle cells According to Glaser (1924), whose findings agree in general with those of earlier investigators partic-

ularly Lapinsky (1905), slender varicose fibers arising from the plexus in the media ramify among the muscle fibers and give rise to short branches some of which terminate in small bulb-like enlargements on the muscle fibers, others apparently end in the musculature without terminal enlargements In addition to the fiber terminations in direct relation to the muscle cells, Woollard (1928) described nerve fiber terminations in relation to certain large branching cells which exist in the media both in the larger and smaller vessels These cells are not regarded as nervous elements but probably are related to the so-called Rouget cells Woollard suggested that they may play a part in vascular reactions According to Boeke

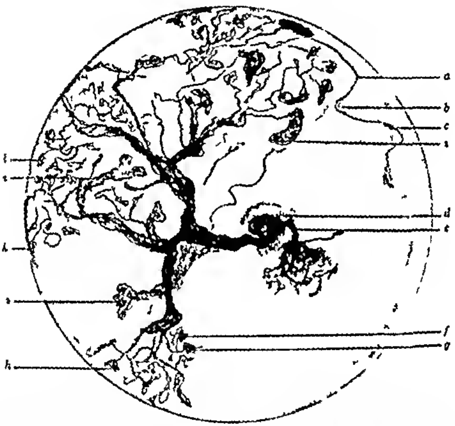


Fig 44 —Terminations of fibers of the carotid sinus nerve in the wall of the carotid sinus Type I according to Sunder Plassmann (1930) *a* Fine nerve fiber with varicosities (*b c*) *d* coarse unmyelinated nerve fiber emerging from myelin sheath *g h k l* terminal structures *i* terminal nets (Ztschr f d ges Anat courtesy of Julius Springer Berlin)

(1932, 1933), the functional connections of the efferent nerve fibers with the musculature of the blood vessels consist mainly of very slender processes arising from the intramuscular plexus which penetrate the muscle cells and become continuous with elements in their cytoplasm

Capillary Innervation —Nerve fibers associated with capillaries have been described repeatedly but there is no general agreement regarding the exact anatomical and functional relationships of such fibers to the capillary wall Nerve fibers in close proximity to capillaries have been described and illustrated by many investigators but only a few have described structural relationships which could be interpreted as mechanisms through which nerve impulses are transmitted to the capillary walls

In a study of preparations of the human heart and bladder, Stoehr, Jr (1926) obtained results which he interpreted as supporting the assumption that unmyelinated nerve fibers not only terminate on the capillary endothelium but frequently also effect contact with endothelial cells through enlargements or flattened expansions of the nerve fibers along their courses He advanced the opinion that capillaries are functionally innervated through specialized terminal structures and modified portions of nerve fibers which lie in contact with the endothelial cells but reiterated his earlier conviction that the capillaries within the substance of the central nervous system are devoid of nerves, although he had previously

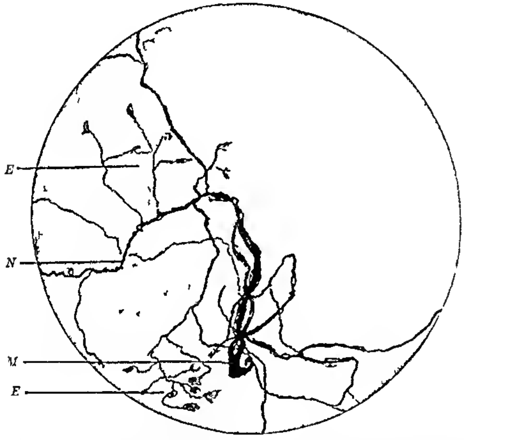


FIG 45 —Terminations of fibers of the carotid sinus nerve in the wall of the carotid sinus Type II according to Sunder Plassmann (1930) *E* Fine branches with terminal plates *M* unmyelinated terminal portion of a myelinated nerve fiber *N* branch of *M* (Ztschr f d ges Anat courtesy of Julius Springer Berlin)

(1922) described terminations of unmyelinated nerve fibers on the endothelium of capillaries in the pia mater

The nerve fibers in proximity to the capillaries lie in intimate contact with the capillary wall for but short distances They commonly run a somewhat tortuous course, coming in contact with the capillary wall only at certain points Not infrequently the nerve fiber is broad and flattened at these points and the neurofibrils are more loosely aggregated than at other points Stoehr, Jr advanced the opinion that the nerve fibers are functionally related to the capillaries at these points of contact and that these contacts play a more significant rôle in the innervation of the capillaries than the specialized nerve fiber terminations Like certain earlier

investigators including Natus (1910) and Ohno (1921), he observed actual nerve fiber terminations on capillaries in relatively few instances.

The results of more recent anatomical investigations afford no significant additional data in support of the assumption that nerve fibers actually effect functional contacts with capillaries. Clark (1929) and Penfield (1932) failed to demonstrate nerve fibers in relation to the capillaries in the substance of the brain and spinal cord although the nerve fibers in the walls of the intramedullary arteries and arterioles were well impregnated in their preparations. Burns (1935) described nerves in relation to capillaries in the hind limb of the cat but found no evidence of actual nerve endings on the capillary endothelium. Nonidez (1936) described the innervation of the blood vessels in the dog's tongue in considerable detail. He also found no anatomical evidence of capillary innervation. Jones (1936) on the contrary interpreted his findings as supporting the assumption that nerve fibers actually terminate in relation to the capillaries.

The capillary wall contains no contractile tissue comparable with the musculature of the arteries and veins. The Rouget cells which are quite generally associated with the capillaries in the Amphibia have been regarded as the contractile elements through which diminution in the caliber of the capillaries is brought about (Krogh, 1922). Similar cells have been observed in association with capillaries in mammals. Rouget described such cells associated with capillaries in the retina and fatty tissue in rabbits and certain ruminants. Vimtrup (1922) found cells which he regarded as Rouget cells associated with the capillaries in the intestine of the mouse and in the interstitial and cutaneous connective tissue in man. King (1939) reported Rouget cells associated with capillaries in the heart of the rat. In spite of these scattered findings, the data available at present do not warrant the conclusion that Rouget cells are associated with all the capillaries in mammals. Neither has it been demonstrated beyond question that they are the essential contractile elements through which capillary contraction is brought about even in the Amphibia. As observed by Clark and Clark (1925), capillary contraction may take place in the Amphibia quite independently of the Rouget cells. On the other hand Bensley and Vimtrup (1928) observed actual contraction of the Rouget cells on the capillaries in the tongue of the living frog and in the surviving nictitating membrane. Contraction of these cells in the latter tissue was elicited by repeated electrical stimulation. Beecher (1936) also reported spontaneous contractions of Rouget cells observed in a transparent chamber in the rabbit's ear. Bensley and Vimtrup, by means of supravital staining with Janus green B, demonstrated myofibrils in the Rouget cells which react to the stain in the same manner and at the same time as those in the muscle cells in the walls of the arterioles. As observed by King (1939) in preparations of the rat's heart, some Rouget cells are supplied with nerve fibers but most of them are not. These observations strongly suggest that the Rouget cells when present, play a rôle in capillary contraction. Jones (1936) on the contrary, regarded them as components of the nervous system but not as contractile elements.

The nerve fibers which are most intimately associated with the capillaries are of smaller caliber than those in the adventitia of arteries and veins which generally are regarded as afferent and most of them are unmyelinated. They also remain intact in the corresponding area after

degeneration of the fibers of spinal origin following section of both dorsal and ventral nerve roots between the spinal ganglion and the communicating ramus (Kuntz, 1927), consequently, they must be regarded as fibers of sympathetic origin

Physiologic Data —Nervous vs Humoral Regulation —The functional control of the blood vessels depends in part on nerve impulses and in part on the effects of hormones and other substances carried in the blood The caliber of the blood vessels must play an important role in the functional state of the tissue or organ supplied by virtue of its effect on the rate of the interchange of substances between the blood and the tissue elements This rate varies both with changes in the volume of blood in the tissue and changes in the rate at which the blood flows The volume of blood supplied to an organ in a given unit of time must vary directly with the caliber of the vessels That the caliber of the vessels supplying an organ usually is increased while the organ is physiologically active and diminished while it is at rest is a fact of common observation To what extent these changes depend on nerve impulses and to what extent they represent the direct effect on the blood vessels of products of metabolism arising due to the activity of the organ is not known The vascular dilatation observed in active organs usually involves the capillaries to a greater extent than the arteries and veins The changes in caliber which the capillaries undergo under normal physiological conditions are due in part to nerve impulses and in part to other influences Direct responses of capillaries to nerve stimulation cannot be denied

The vasoconstrictor mechanism probably plays a dominant role in the nervous control of the blood vessels Inasmuch as the vasoconstrictor fibers are conveyed to the blood vessels in the same nerves which also convey other fibers, the effect of impulses conducted by the other fibers is not always apparent when the nerve trunk is stimulated For example, stimulation of the fibers supplying a gland may inhibit secretion due to the constriction of its blood vessels elicited by stimulation of the vasoconstrictors, even though secretory impulses are reaching the gland cells On the other hand, changes in the caliber of the blood vessels may follow stimulation of a nerve, though quite independently of vasomotor impulses For example, stimulation of a nerve supplying skeletal muscle usually results in dilatation of the blood vessels in the muscle by virtue of the effects of metabolic products arising as a result of muscle contraction If the muscle is curarized so that the motor terminations are paralyzed stimulation of the nerve is followed by little or no dilatation of the blood vessels Dilatation of blood vessels which follows nerve stimulation is in many cases only indirectly dependent on nerve impulses, consequently, it does not in such cases demonstrate the existence of vasodilator fibers Most arteries and veins probably are supplied with both vasoconstrictor and vasodilator nerve fibers

Vasomotor Nerves —Vasoconstrictor activity is mediated mainly through the sympathetic nerves This is evidenced by the fact that all arteries and veins, with few possible exceptions, constrict in response to stimulation of their sympathetic nerves Since, as pointed out above nerve fibers extending from the plexuses on the aorta along the peripheral arteries play no part in the innervation of the distal portions of these arteries, the vasoconstrictor fibers must be conveyed peripheralward mainly through

the somatic nerves, and reach the peripheral vessels through rami which join them at intervals throughout their entire extent

When the vasoconstrictor fibers supplying a given area are severed the blood vessels in this area immediately dilate This result probably is due to the removal of tonic impulses which normally flow out to the vessels in a more or less constant stream and maintain the musculature of the vessels in a state of tonus After an interval which varies in different animals and at different times in the same animal vessels deprived of their vasoconstrictor innervation regain tonus in some degree and may become actually smaller in caliber than the normally innervated vessels of the opposite side, even before regeneration of the vasoconstrictor fibers could have taken place Since there are no ganglion cells along the walls of the peripheral arteries, it must be assumed that the musculature of the vessels develops a certain degree of tonus in the absence of nerve impulses, probably due to a reaction of the musculature of the vessels to vasoconstrictor substances in the blood If only the preganglionic fibers are cut, leaving the sympathetic cells and fibers intact, the vessels regain tonus more promptly than if the postganglionic fibers are severed (Boshamer, 1925) This observation suggested to Schilf (1926) that the ganglion cells exert some influence on the musculature of the vessels even in the absence of preganglionic connections Vasoconstrictor substances such as adrenin circulating in the blood undoubtedly play a rôle in the restoration of vascular tonus following section either of the preganglionic or postganglionic vasomotor nerve fibers Although tonus is restored more promptly following section of the preganglionic fibers, the tonic reaction of the vascular musculature to adrenin in the circulating blood is more marked following section of the postganglionic fibers

Stimulation of a peripheral nerve which includes both vasoconstrictor and vasodilator fibers, under certain conditions, elicits not constriction but dilatation of the vessels affected If, for example the sciatic nerve is cut, stimulation of its peripheral end commonly elicits vasoconstriction throughout the portion of the limb affected If, after several days, the peripheral end of the sciatic again is stimulated, the observed result may be vasodilatation and not vasoconstriction It has been assumed that this result is due to the fact that the vasoconstrictor fibers undergo degeneration more rapidly than the vasodilator fibers These results not only suggest a method of investigation by which the distribution of vasodilator fibers can be determined but also indicate an inherent difference in the vasoconstrictor and vasodilator fibers

Central Vasoconstrictor Pathways —The preganglionic vasoconstrictor fibers, as stated above, emerge from the spinal cord in the thoracic and upper lumbar regions Impulses conducted by these fibers exert a constant tonic influence on the blood vessels If the spinal cord is transected in the cervical region, the blood vessels at once lose tonus and become markedly dilated particularly in the splanchnic and cutaneous areas The tonic impulses obviously are conducted downward from the brain stem

The vasoconstrictor center may be stimulated reflexly by afferent impulses conducted by sensory components of any spinal nerve and certain of the cranial nerves On the basis of experimental studies Ranson (1916) pointed out that afferent impulses which initiate pressor reflexes are conducted by fibers which enter the dorsolateral funiculus of the spinal cord

through the lateral divisions of the dorsal nerve roots, run but a short distance in this funiculus and probably terminate in the substantia gelatinosa in the dorsal gray column. The pressor impulses probably are conducted upward in the cord through a series of short fibers which take origin in the substantia gelatinosa and run in the dorsolateral funiculus. They are conducted upward on both sides but somewhat better homolaterally. The corresponding efferent spinal vasomotor pathways are located either in the ventral or lateral funiculi. They are not interrupted by section of the dorsal funiculi and the dorsal gray columns. In man, according to Marquis and Williams (1938), somatic afferent impulses which elicit reflex vasomotor responses are conducted upward in the spinothalamic tracts. The vasomotor reflex arcs are completed in the brain stem below the thalamus. Vasoconstrictor reflexes also are carried out through reflex centers in the spinal cord (Ranson and Billingsley, 1916, Brooks, 1933).

The differential effects of reflex vasoconstrictor stimulation support the assumption that the neurons in different parts of the vasoconstrictor center are connected, by definite aggregates of fibers, with the vasoconstrictor neurons which supply various regions of the body. For example, some of the neurons control the activities of the vessels of the skin, others are concerned with those of the vessels of the splanchnic area. The neurons in different parts of the center apparently may also be acted upon separately, at least under normal physiological conditions.

Vasodilator Nerves.—Certain parasympathetic nerves are known to include vasodilator fibers but a general distribution of such fibers throughout the parasympathetic system is not universally conceded. Stimulation of the chorda tympani elicits vasodilatation in the tongue, indicating the existence of vasodilator fibers in the nerves arising from the submaxillary ganglion (Anrep and Evans, 1920). Physiologic data also indicate the existence of preganglionic vasodilator fibers in the glossopharyngeal and the sacral parasympathetic nerves. Conclusive evidence of the existence of vasodilator fibers in various other parasympathetic nerves is not forthcoming.

Certain experimental data have been interpreted as evidence of the existence in the dorsal roots of the spinal nerves of fibers which conduct vasodilator impulses. Stricker (1876) observed vasodilation and a rise of temperature in the dog's foot in response to stimulation of the distal ends of the divided dorsal roots of the sixth and seventh lumbar nerves. This observation was corroborated by Gartner (1889), Morat (1892), Worziloff (1896) and other more recent investigators. Bayliss (1901) reported marked dilatation of the blood vessels of the hind limb in response to stimulation of the dorsal roots of the fifth, sixth and seventh lumbar and first sacral nerves. Since he could observe no degeneration of fibers in these nerves following section of their dorsal roots proximal to the spinal ganglia but did observe fiber degeneration following removal of the spinal ganglia, he advanced the opinion that the vasodilator fibers in question are not true efferent nerve components but are identical with sensory components and subserve vasodilatation by virtue of their capacity for antidromic conduction. On the basis of further experimental data, he concluded that vasodilator fibers to the fore limb of the dog traverse the dorsal roots of the sixth, seventh and eighth cervical and first thoracic

nerves Langley (1901) also interpreted vasodilatation in the hind limb in response to stimulation of the dorsal roots of the lower lumbar nerves as the result of antidromic conduction.

On the basis of an intensive study of the reaction of the blood vessels to stimulation of dorsal root fibers, Bayliss concluded that this reaction involves a relatively long latent period (two to eight seconds in the dog) and exhibits a long after-effect. According to his observations vasodilatation may persist ten minutes or longer after the stimulus has been removed. This seems to be characteristic of antidromic stimulation. According to Hinsey and Gasser (1930) vasodilator impulses resulting from stimulation of the dorsal nerve roots in the cat are mediated solely by fibers which conduct at the rate of about 2 meters per second and are responsible for the C-wave of the action potential picture.

Langley (1923) pointed out that the distribution of the antidromic fibers through a peripheral nerve coincides with its sensory distribution. Having determined the exact distribution of certain cutaneous nerves, he studied the effect of stimulation of the dorsal nerve roots following section of certain cutaneous branches. For example after section of the superficial ramus of the median plantar nerve in the cat stimulation of the dorsal root of the seventh lumbar nerve, from which the fibers of the median plantar nerve are derived, no longer elicited vasodilatation in the corresponding cutaneous area. This result seems to support the theory, advanced by Bayliss that the antidromic fibers which mediate vasodilator impulses, like the sensory fibers arise from spinal ganglion cells.

If the antidromic fibers which, under experimental conditions conduct vasodilator impulses were physiologically antagonistic to the vasoconstrictor fibers we should expect that, following section of the dorsal root fibers leaving the ventral roots and communicating rami intact the blood vessels involved would exhibit diminution in caliber due to the absence of the inhibitory impulses conducted by the antidromic fibers. This has not been observed. Section of the dorsal root fibers apparently does not alter the tonus or caliber of the blood vessels after the effect of the primary stimulation caused by section of the fibers has subsided. Antidromic conduction probably plays no part in the maintenance of the normal tonus of blood vessels. There is no conclusive evidence that it is a normal physiologic process. As pointed out above the reactions of the vessels to antidromic stimulation differ from their reactions to sympathetic stimulation in that they manifest a longer latent period as well as a delayed after effect. Furthermore second and third stimulations of the antidromic fibers usually are less effective than the first. These facts indicate that the muscle cells react to antidromic stimulation according to a different mode than to sympathetic stimulation. On the basis of the humoral theory of nerve conduction, this difference could be explained on the assumption that the substance liberated at the periphery by antidromic stimulation of dorsal root fibers differs from that liberated by stimulation of sympathetic fibers. Data reported by various investigators, particularly Lewis (1927) Bena (1931) and Wayne (1931) indicate that vasodilatation due to antidromic stimulation depends on the liberation of histamine like substance at the periphery. On the basis of all the data available Dale (1929) advanced the theory that the first substance liberated at the periphery as a result of antidromic stimulation or local injury is histamine which directly

causes dilatation of the minute blood vessels with which it comes in contact and acts as a persistent stimulus to the sensory endings. The impulses engendered in the sensory endings traverse collateral branches of the sensory fibers and act upon the arterioles, thus liberating acetylcholine as the effective vasodilator substance. The blood flowing through vessels which are under the influence of antidromic stimulation also acquires vasodilator properties (Kibjakow, 1931).

Langley advanced the theory that antidromic impulses affect particularly the smaller arteries and capillaries. He did not believe that they affect the arterial musculature directly but maintained that either the afferent fibers sustain some peculiar relationship to the capillaries or vasodilatation, following stimulation of the antidromic fibers, is an indirect result of nerve impulses. Bayliss expressed the opinion that afferent fibers bifurcate near the periphery and that one branch terminates in sensory end organs in the skin or muscle while the other terminates in the musculature of an arteriole. Neither of these views has found anatomic verification. The view that nerve fibers give rise to terminal branches which differ functionally, furthermore, is not in harmony with current physiologic concepts of the neuron. Data are not wanting which seem to indicate quite clearly that impulses received at the periphery may be conducted centralward to the location of the assumed bifurcation and from that point via the vascular branch to a blood vessel in which they elicit dilatation. Stimulation at the periphery also may elicit local vasodilatation even after section of the afferent fibers proximal to the location of the assumed bifurcation. It seems not improbable that local erythema may involve a peripheral mechanism of this kind.

In spite of the evidence in support of the theory of the antidromic conduction of vasodilator impulses, the opinion that vasodilator fibers which emerge through dorsal spinal nerve roots arise from nerve cells in the gray matter in the spinal cord has been advanced repeatedly. Anatomical proof of the existence of efferent fibers in the dorsal nerve roots, however, is not forthcoming.

The concept of sympathetic vasodilator nerve fibers is not new, but it has played no significant role in physiologic teaching regarding vasomotor regulation until relatively recently. Dastre and Morat in 1880 observed dilatation of the vessels in the buccal cavity, the mucous membrane of the palate, gums and lips and the skin of the lips and cheeks in response to stimulation of the cervical sympathetic trunk in the dog. The tongue and the ear simultaneously became pale due to vasoconstriction. Langley and Dickinson (1890) reported similar effects of cervical sympathetic stimulation.

Dale's (1906) classical account of the action of ergotoxine has an important bearing on the concept of sympathetic vasodilators. He observed that the purely inhibitory effects of sympathetic stimulation are unaffected by this drug, whereas motor effects are either abolished or reversed. He advanced the conclusion that when motor responses are abolished by ergotoxine the innervation is purely motor, but when motor responses are reversed the sympathetic supply includes both motor and inhibitory fibers, and that the reversal is due to paralysis of the motor component. After the administration of ergotoxine in his experiments, either stimulation of the splanchnic nerves or injection of adrenin resulted in a fall in blood

pressure He therefore, concluded that the sympathetic nerves in question include vasodilator fibers which are normally masked by the vasoconstrictor fibers That the depressor action of splanchnic stimulation was not due to liberation of adrenin is indicated by the results of later experiments (Dale 1913) in which stimulation of the splanchnic nerves, after full doses of ergotoxine, produced slight depressor effects in adrenalectomized animals Pierce (1913) observed in perfusion preparations that adrenin produces an effect similar to that of ergotoxine noted above when the perfusion liquid contains no calcium Bauer and Fröhlich (1918) advanced the theory that dilatation of the vessels, in such experiments, is elicited by stimulation of vasodilator fibers following paralysis of the vasoconstrictors by the action of the drugs employed Schilf, Feldberg and Hahn (1926) also elicited dilatation of perfused vessels by sympathetic stimulation following the administration of adrenin in appropriate doses

Weak electrical stimulation of the splanchnic nerves may result in dilatation of the corresponding vessels in the absence of paralysis of the constrictor nerve endings This effect probably is due to the discharge of adrenin in minute quantities (Cannon and Lyman, 1913) and cannot be regarded as proof of the existence of vasodilator fibers in these nerves

The vasodilator action of adrenin in minute doses was first described in the dog by Moore and Purinton (1900) The reversal of the normal action of adrenin by administration of ergotoxine as observed by Dale, suggested that the two dilator effects may be identical in character and that the action of adrenin in small doses, in the absence of ergotoxine, might indicate the distribution of vasodilator nerve fibers Hartman (1915) advanced experimental data in support of the assumption that in the cat a discharge of adrenin normally produces constriction in the splanchnic vessels and dilatation in the peripheral circulation The peripheral dilatation according to Hoskins Gunning and Berry (1916), takes place in the muscles rather than in the skin Rosenblueth and B Cannon (1933) also reported experimental data which indicate that, in the cat vasodilatation in response to adrenin in small doses occurs more readily in certain parts of the muscular system and the skin than in the intestine

The effect of adrenin on the intestinal vessels according to Goetz (1939), varies with the dosage employed Minute doses result in increasing the flow in these vessels Larger doses cause a feeble and transient early constriction followed by prolonged dilatation Goetz detected no relation of the effect of adrenin on the intestinal vessels to the course of the blood pressure response On the basis of his experiments, he advanced the opinion that adrenin acts as a blood distributor rather than as a blood pressure augmentor hormone The intestinal vessels obviously do not contribute materially to the rise in blood pressure following the injection of adrenin Neither is this rise due solely to constriction of the cutaneous vessels but mainly to increased cardiac activity

In rats under urethane anesthesia, Wyman and Tum Suden (1932) observed a depressor action of adrenin in small doses only in the absence of the adrenal medulla but after the administration of cocaine this action was reversed (Wyman and Tum Suden 1935) After exclusion of the splanchnic circulation the pressor effect of adrenin in larger doses was reduced After administration of ergotoxine the action of adrenin was reversed and the depressor effect was not altered by exclusion of the

splanchnic vessels (Wyman and Tum Suden, 1936) They concluded on the basis of these experimental data that in the rat vasoconstrictor fibers are more abundant in the splanchnic area than in the skeletal muscles and the skin and that vasodilator fibers are uniformly distributed in both systems In experiments on the cat reported by Clark (1934), intra-arterial injections of adrenin (0 05γ) resulted in increased outflow of blood from the veins of the leg muscles and constriction of the cutaneous vessels Bulbring and Burn (1936) recorded an increased outflow from the saphenous vein in dogs under ether but pointed out that this may have been due to venous constriction rather than arterial dilatation, since the outflow was not increased by adrenin in any dosage following the administration of ergotoxine In experiments on dogs reported by Rein and Schneider (1931) and Mertens, Rein and Valdecasas (1936), adrenin injected intravenously caused an initial increase in the flow of blood followed by a decrease in resting muscle but, during muscular contraction when the blood flow was increased, adrenin caused only a slight further increase In a somewhat similar investigation, Bulbring and Burn (1938) observed that adrenin injected intra-arterially in muscles of the dog's hind leg perfused with defibrinated blood caused diminution of the inflow during prolonged tetanus as during rest but in a lesser degree In Clark's (1934) experiments on cats, adrenin in small doses injected intra arterially always resulted in vasoconstriction in the intestine, but after administration of ergotoxine it resulted in vasodilatation in the intestine Burn (1936) reported vasodilatation in the intestine of the dog due to adrenin injected intravenously or intra arterially both before and after administration of ergotoxine

Lewis and Pickering (1931) have advanced certain experimental data which seem to prove the existence of vasodilator as well as vasoconstrictor fibers in the sympathetic nerves in the extremities in man They devised an experimental procedure in which vasodilatation in the hands was produced by raising the temperature of the body In order to eliminate the direct effect of heat on the hands, the subject was seated in a warming chamber arranged so that the head and neck and the hands were unenclosed By this means the temperature to which the body is exposed may be raised to any desired degree while the hands are exposed to room temperature If a large rise in the skin temperature of the hands is desired, it is essential to start with the hands cold, *i e*, the room temperature must not be above 14° to 16° C If the room temperature is 18° C or over, the hands usually are warm, and further warming of the body does not result in a considerable rise in the skin temperature of the hands

In experiments reported by Hibben and Landis (1932), immersion of the forearms of normal subjects in warm water (43° to 45° C) resulted in vasodilatation in the lower extremities Immersion of one forearm or one leg in warm water also resulted in vasodilatation in the other extremities The rise in the skin temperature of the toes became apparent within fifteen minutes after immersing the forearms The vasodilator response, in these experiments, apparently depended on the return of the warmed blood from the immersed extremities

When the extremities of normal subjects are naturally cool, according to Pickering and Hess (1933), vasodilatation in response to warming the body becomes evident in the fingers earlier than in the toes In some

instances vasodilatation may fail in the feet. They have attributed the delayed response in the toes as compared with the fingers, not to a difference in time but to the difference in the intensity of the vasomotor relaxation in the upper and lower extremities. Warming of the body elicits complete relaxation of the vessels in the upper extremities but only incomplete relaxation of those in the lower extremities.

The rise in skin temperature of the hands in response to warming the body according to Grant and Bland (1929), depends on the responsiveness of the arteriovenous anastomoses in the distal parts of the fingers to changes in body temperature. These anastomoses become constricted as the body is cooled and dilate as the body temperature rises. The curves of skin temperature of the normally innervated hand obtained in the experiments of Lewis and Pickering rise slowly at first, then more rapidly and gradually round off into a plateau. That the vasodilatation involved in the warming of the hands in these experiments was effected through the sympathetic nerves is indicated by the fact that warming of the body did not elicit similar responses in hands deprived of their sympathetic innervation. That it is an active process and not the result of inhibition of vasoconstrictor impulses also is demonstrated by the results of experiments involving paralysis of certain peripheral nerves. For example in patients with Raynaud's disease the temperature of the fifth finger did not rise following narcotization of the ulnar nerve although warming of the bodies of the same patients, the hands remaining exposed to cold, resulted in conspicuous vasodilatation in the hands and a marked rise in their skin temperature.

The mechanism of the inhibitory action of the vasodilator nerves, according to Bozler (1936) can be explained most satisfactorily on the assumption that the actions of vasoconstrictor and vasodilator impulses are mediated by neurohormones which inactivate each other. Contraction in response to stimulation of vasomotor nerves is determined by the excess of the vasoconstrictor substance.

The data available at present prove the existence of sympathetic vasodilator fibers in man and various laboratory animals but there are significant differences in their abundance in different species and in various parts of the body in the same species. In the muscles of the dog the sympathetic vasodilator fibers are cholinergic and may be readily demonstrated without the use of ergotoxine. The cutaneous nerves in the dog probably include no vasodilator fibers except in the ear. The sympathetic supply to the intestine includes some vasodilator fibers, presumably adrenergic, which may be demonstrated following administration of ergotoxine. In the monkey and the rabbit the vessels in the skeletal muscles are not supplied with vasodilator fibers. In the cat the sympathetic supply to these vessels includes a few vasodilators (Burn, 1938). A sympathetic vasodilator innervation of the cutaneous vessels in man is indicated by the data reported particularly by Lewis and Pickering and their collaborators but certain data advanced by Uprus, Gaylor and Carmichael (1936) do not fully support this assumption.

Pressoreceptive Reflex Mechanisms.—Hunt (1895) showed under carefully controlled conditions that depressor reflexes may be elicited by stimulation of most any afferent nerve. Not uncommonly when a nerve is chilled the same stimulus which before elicited a fall in blood pressure

elicits a rise. Very weak stimulation of any afferent nerve, except perhaps the splanchnic, almost invariably elicits depressor reflexes, while strong stimulation of any afferent nerve, except the so-called depressor nerve and the carotid sinus nerve, elicits pressor reflexes. These facts have given rise to the assumption that there are two kinds of afferent vasomotor fibers which have been called pressor and depressor nerve fibers respectively.

The differences in the vasomotor responses elicited by weak and strong stimulation of afferent nerves, according to Ranson and Billingsley (1916), can readily be explained by the difference in the resistance to afferent conduction offered by the respective central pathways employed. According to their findings the depressor impulses are conducted upward in the ventral parts of the lateral funiculi of the spinal cord through paths composed of long fibers with few relays, whereas the pressor impulses are conducted upward at the apices of the dorsal gray columns through paths composed of short fibers with frequent relays. The resistance of the latter pathways is relatively high as compared with that of the former. Weak impulses reaching the spinal cord are conducted upward in the depressor path and result in vasodilatation and a fall in blood pressure. Whether they also inhibit the tonic action of the vasoconstrictor center is not clear. Within a certain range of stimulation, constriction and dilatation balance each other with little change in pressure. Vasodilatation probably is masked rather than inhibited. As stimulation becomes stronger, impulses ascend in the pressor paths in sufficient volume to bring about vasoconstriction and a consequent rise in blood pressure. It is quite unnecessary to assume inhibition of a vasodilator center in any case, since the action of the vasoconstrictor fibers is more powerful than that of the vasodilators.

Stimulation of the trigeminal nerve elicits vasomotor reactions comparable to those elicited by stimulation of the spinal nerves. This nerve contains somatic afferent fibers whose central connections are comparable with those of the somatic afferent fibers of the spinal nerves. Its pressor and depressor reactions, therefore, can be explained on the same basis.

The pressoreceptive mechanisms associated with the cardio-aortic zone and the carotid sinuses play a peculiarly significant role in the cardiovascular regulation. When the endovascular pressure rises in the left ventricle and the arch of the aorta impulses conducted centralward in the depressor nerves elicit reflex slowing of the heart and peripheral vasodilatation. When the endovascular pressure falls the pressoreceptors in this area are no longer stimulated; consequently, the cardiac rhythm is accelerated and peripheral vasoconstriction takes place. These reflex reactions tend to maintain normal blood pressure. Likewise variations in the carotid sinus zone result in immediate cardiovascular reactions. A rise in the endovascular pressure in this zone elicits reflex slowing of the heart and a fall in blood pressure in the general circulation. Conversely reduction in the endovascular pressure in the carotid sinus results in cardiac acceleration and a general rise in blood pressure.

In experiments carried out to determine whether carotid sinus reflexes play a part in vasomotor regulation when the systemic pressure is low Sweeney (1940) found that, in dogs under chloralose anesthesia, lowering of the blood pressure to sustained low levels of 45 to 70 mm. of mercury elicits no pressor activity in the carotid sinuses. Such activity, if present would be indicated by a fall in blood pressure when the carotid sinus nerves

are cut. In ten of fifteen experiments, denervation of the carotid sinuses while the systemic blood pressure was at a sustained low level resulted in a gradual rise in pressure, indicating the presence of depressor activity at the time of denervation.

The pulmonary veins, the venae cavae and the right atrium constitute a pressoreceptive zone sensitive to changes in venous pressure. Experimental data reported by Bainbridge (1916) and McDowall (1934) support the assumption that reflexes initiated in this zone by changes in venous pressure may play a rôle in the regulation of cardiac rhythm and vascular tonus.

Stimulation of receptors in the pulmonary artery by increased pressure in the pulmonary arterial system, according to Schweigk (1935), results in reflex bradycardia and arterial vasodilatation. Lowering of pulmonary arterial pressure results in cardiac acceleration and increased arterial tonus.

Certain experimental data reported by Heymans *et al.* (1936) indicate that the vascular area comprising the celiac and mesenteric arteries also may be regarded as a pressoreceptive zone. They observed proprioceptive regulation of vascular tonus in spinal dogs brought about through pressoreceptive reflexes originating mainly in the organs supplied by the celiac and mesenteric arteries and secondarily in the area of distribution of the thoracic arteries. The mesenteric pressoreceptors probably are mainly Pacinian corpuscles (Gammon and Bronk, 1935).

Since pressoreceptive zones are known to exist in these several vascular areas the question arises: are all blood vessels endowed with pressoreceptors? The available experimental data suggest a negative answer. The general vascular tonus is regulated through reflexes initiated in pressoreceptors in certain well localized areas: the carotid sinus and the cardio-aortic, veno-atrial, pulmo-arterial and thoracosplanchnic zones. Evidence of the initiation of similar reflexes in other vascular areas is not forthcoming. By the use of a balloon in the larger blood vessels Knap (1929) elicited reflex changes in blood pressure by changes in the internal pressure in the arch of the aorta and the carotid sinus but not in other parts of the large vessels. In experiments reported by Kuntz and Saphir (1933), stimulation of the aorta and pulmonary artery except in the region of the plexus in which the depressor nerve terminates failed to elicit reflex changes either in blood pressure or heart-rate. A decrease in blood pressure in other vascular areas may elicit local or regional vasomotor reactions which are not involved in the pressoreceptive regulation of the general blood pressure.

Chemoreceptive Reflex Mechanisms.—The distribution of chemoreceptors and pressoreceptors overlaps in the cardio-aortic zone but neither kind of receptor is equally abundant throughout the entire zone. The proximal portion of the aorta and the adjacent areas comprise mainly pressoreceptors; the carotid sinuses and the carotid and aortic bodies, mainly chemoreceptors. The chemoreceptors connected with the carotid sinus nerve, consequently, exceed the pressoreceptors connected with this nerve whereas the pressoreceptors connected with the vagi exceed the chemoreceptors. Chemical stimulation undoubtedly plays a more significant rôle in reflex vasomotor regulation through the carotid sinus nerves than through the vagi (Bouckaert *et al.*, 1938). Increased activity of the chemoreceptors results in increased activity of both the vasomotor and respiratory centers. Decreased activity produces opposite effects. The increased

activity of the centers is due to the positive stimulating effect of nerve impulses reaching them from the chemoreceptors through the corresponding afferent nerves. In summarizing the experimental data bearing on the nature of stimuli to which the chemoreceptors respond, Schmidt and Comroe (1940) pointed out that the results obtained by all who have acquired the requisite technic in this field of investigation support the conclusions of Heymans *et al* (1930, 1933) that these end organs are normally stimulated mainly by a fall in pH, a rise in CO_2 tension and anoxemia. The stimulating effects of anoxemia on both circulation and respiration probably are due mainly to reflexes initiated in the chemoreceptors (Schmidt and Comroe, 1940). Direct effects exerted on the vasomotor and respiratory centers are not precluded but the threshold of stimulation of the chemoreceptors by anoxemia is lower than that of the centers. Stimulation of the chemoreceptors by anoxemia also elicits more rapid and more vigorous responses than those resulting from central anoxemia. Excessive CO_2 tension, on the contrary, exerts its influence on blood pressure mainly through its stimulating effect on the vasomotor center (Lambert and Gellhorn, 1938).

Reflex Regulation of Blood Pressure.—The blood probably never is distributed uniformly throughout the body but is present in any given region in greater or lesser abundance according to the requirements of the organs and tissues in question or the maintenance of constant body temperature. Under changing conditions, particularly of external temperature, considerable volumes of blood are displaced from the peripheral to the splanchnic area and *vice versa*. When the external temperature is low, the volume of blood circulating in the peripheral vessels is greatly reduced in order to prevent too great loss of heat, and that circulating in the splanchnic vessels is correspondingly increased. On the contrary, when the external temperature is high, the volume of blood in the peripheral vessels is increased while that in the splanchnic vessels is correspondingly decreased. The nutritive requirements of the tissues under changing conditions also necessitate changes in the distribution of the blood. For example, the volume of blood circulating through the skeletal muscles is markedly increased during muscular exercise.

In experiments carried out on human subjects, Alam and Smirk (1937, 1938) demonstrated a blood pressure raising reflex elicited by the stimulating effect of metabolites liberated in skeletal muscles during muscular exercise. They regarded this reflex as a physiologic device to insure an increased blood supply to the active muscles. Exercise of a limited group of muscles may result in an appreciable rise in blood pressure. Vigorous exercise of the whole body results in a greater rise. If the accumulated metabolites are retained in the muscles, by arrest of the circulation, after the exercise of any group of large muscles, *e. g.*, the leg muscles, the cardiac acceleration and increased blood pressure are maintained above normal as long as the escape of the stimulating metabolites is prevented. The reflex rise in blood pressure does not depend wholly on the bulk of the active muscle. In the normal human subject, exercise of the hand or forearm usually causes a greater rise in pressure than exercise of both lower extremities. The local vasodilatation in active muscles is not mediated through the sympathetic nerves but is due to the direct stimulating effect of the accumulated metabolites (Grant, 1938). Sustained contraction of the

muscles compresses the vessels but does not prevent their dilation and an *increased flow* of blood through the muscles. After exercise of any group of muscles the flow of blood is still further increased, the degree of the resulting hyperemia and its duration is determined by the vigor of the exercise and the length of the interval during which it was maintained. The administration of adrenin in small doses, according to Grant and Pearson (1938), causes an increase in the flow of blood in the human forearm and leg and an increase in the limb volume due to vasodilatation in the voluntary muscles. The vasodilator effect of adrenin, in their experiments, was increased after sympathectomy.

The maintenance of constant blood pressure during the redistribution of the circulating blood and the loss of blood by hemorrhage involves marked vasoconstriction in extensive vascular areas and changes in the volume of certain organs, particularly the spleen and the liver. The *spleen, according to Barcroft and Stephens (1927), plays an important* role both in the redistribution of the circulating blood and the maintenance of constant body temperature. They demonstrated a reduction in the size of the spleen to one-third its initial volume during muscular exercise and a still greater reduction during severe hemorrhage. The volume of blood squeezed out of this organ in experimental animals, according to their observations, may equal one-fifth of the volume of the circulating blood. According to Barcroft and Nisimaru (1932), the undulatory waves of blood pressure which ordinarily have a duration of about forty-five seconds but vary from twenty-five seconds upwards, are due mainly to the rhythmic contractions of the spleen. The liver under certain conditions also undergoes reduction *in size*, consequently releasing blood into the general circulation. According to Grab, Janssen and Rein (1929), the liver, under the action of adrenin, may release a volume of blood equal to one-half its normal size. By reason of their capacity to undergo changes in size, the spleen and liver may be regarded as reservoirs of blood which may be added to the circulating blood whenever the necessity arises. The reduction in the size of the spleen is brought about by contraction of its own musculature under the influence of nerve impulses. The reduction in the size of the liver, according to Rein and Roszler (1930), is conditioned by constriction of the splanchnic vessels, resulting in diminution of the volume of blood entering the liver through the portal vein. In experiments reported by Eckhardt (1935), splanchnic stimulation resulted in an increase in the outflow into the vena cava but a decrease in the flow of blood into the liver. Inasmuch as the outflow from the liver is not impeded, the volume of blood in the liver is diminished and the organ is reduced in size. Vasoconstriction accompanying the loss of blood does not take place equally throughout the body but usually is more marked in the splanchnic than in the peripheral area. Rein and Roszler (1930) also pointed out that vasoconstriction associated with diminished blood volume is most marked in the vascular fields in which the vessels already are constricted in the interest of temperature regulation, whereas a lesser degree of vasoconstriction takes place in fields in which the vessels are dilated in the interest of temperature regulation. They pointed out that the responsiveness of the peripheral blood vessels is conditioned, in a large measure, by the external temperature and that measurable variations in blood pressure

afford no index of the changes in the distribution or the volume of the circulating blood which may be taking place

The hepatoportal system, including the liver spleen and intestinal tract, constitutes the most extensive and significant blood reservoir in the body and probably plays an important role in all large circulatory adjustments In an experimental study of the responses of this system to various drugs, Katz and Rodbard (1939) have attempted to analyze its effect in the regulation of the circulating blood volume, venous return and the redistribution of blood Their findings indicate that constant and varying shifts occur in the various parts of this system even during ordinary activities the integration of which plays an important role in the coordination of the peripheral circulatory apparatus in response to the requirements of the moment It constitutes a reservoir of large capacity which is delicately attuned particularly to the regulation of the circulating blood volume and the venous return to the heart The liver alone may hold as much as 25 per cent of the total blood volume and the preportal bed, including the spleen and the intestinal tract, another 30 per cent Circulation, therefore, is not necessarily controlled by the heart Under a wide variety of circumstances the reactions of the hepatoportal system undoubtedly exert the major controlling influences

In experiments reported by Rein (1943), occlusion of the hepatic artery in the dog resulted in immediate vasomotor throttling of the celiac and superior mesenteric arteries This reaction was interpreted as a reflex response to stimulation of pressoreceptors in the hepatic artery which is carried out through spinal reflex centers and limited to the gastro-enteric vessels It is independent of other pressoreceptive mechanisms but is augmented by simultaneous carotid sinus stimulation and oxygen deficiency and extinguished by pulmonary hyperventilation It probably represents a protective reflex which tends to maintain an adequate arteriovenous pressure gradient within the liver These experimental findings support the hypothesis that the vasomotor hepatic artery reflex results in a certain degree of antagonism between the blood flow through the hepatic artery and that through the arteries which supply the gastro intestinal canal The latter vessels, therefore, may be regarded as constituting a collateral vasoconstrictor zone for the arterial supply to the liver The response of the gastro intestinal vessels is elicited mainly by lowering of pressure in the hepatic artery, which may be caused or augmented by oxygen deficiency This reflex, therefore, need not be regarded as a compensatory reaction which tends to maintain the general arterial pressure It probably serves primarily to insure an adequate oxygen supply to the liver and aids in regulating the distribution of blood locally

On the basis of experimental studies carried out on dogs, Chauchard, Chauchard and Barry (1931) reported that hemorrhage results in modification of the excitability of the inhibitory mechanism of the heart and the vasomotor mechanisms The chronaxie for all the reactions tested in their experiments was increased by loss of blood to an extent which was roughly proportional to the severity of the hemorrhage Restoration of the blood lost, after defibrination, resulted in almost complete restoration of the excitability of the mechanisms in question to its former level Temporary restoration of the excitability of these mechanisms also could be brought about by injection of a saline solution

The rate at which the blood is propelled through the circulatory system depends in a large measure on the rate and force of the cardiac contractions and the caliber of the blood vessels, particularly the terminal arteries and arterioles. The fact that adrenin following the administration of atropine, causes a reduced flow of blood in spite of a rapid heart but results in a small central blood volume and hastens the velocity of the circulation, according to Hamilton (1932), indicates that the volume of flow is a function of the peripheral vasoconstriction and that the central active blood volume and, in part, the circulation times are functions of the cardiac rhythm. This, in turn, is the resultant of the functional balance between the accelerator and inhibitory nerves to the heart prevailing at the moment. These nerves are activated by afferent impulses emanating from all parts of the body but the inhibitory cardiac nerves are activated particularly by impulses arising in certain circumscribed vascular areas, particularly the cardio-aortic pressoreceptive zone and the carotid sinus. The caliber of the blood vessels is determined by the functional balance between the vasodilator and vasoconstrictor nerves and the pressure exerted by the circulating blood. The vasodilator and under certain conditions the vasoconstrictor nerves also are activated by impulses arising in the cardio-aortic pressoreceptive zone and the carotid sinus. These areas, as stated above, are supplied by special groups of afferent fibers the terminal structures of which are located in the adventitia of the vessels and are stimulated both by internal pressure and chemical substances in the circulating blood.

By means of electrocardiograms obtained from rabbits Niederhoff (1932) demonstrated that action currents in the so-called depressor nerve occur synchronously with the elevations in blood pressure in the aorta due to the cardiac contractions and respiratory movements. In addition to the smaller oscillations there are two larger paired waves with a definite pause between the succeeding pairs. The first of the larger waves coincides with the rapid rise in pressure following ventricular contractions, the second with the first rebound following this contraction. The impulses arising in this manner are conducted by the depressor nerve to the vasomotor center in the medulla oblongata where they are transmitted to the cardiac inhibitory components of the vagus nerves.

Cardiac and vascular reflexes arising in the first part of the internal carotid artery were described by Hering as early as 1923 but their significance in the regulation of cardiac rhythm and blood pressure was not understood until some years later. Experimental procedures designed to delimit the area of the internal carotid artery in which the reflexes in question arise, carried out by Hering and others, have resulted in its localization in the enlarged segment of this vessel near its origin from the common carotid artery, known as the carotid sinus. Cardiac inhibitory reflexes arising in the carotid sinus are mediated through the carotid sinus nerve and efferent components of the cardiac rami of the vagus nerves. Other reflexes arising in the carotid sinus which play a role in the regulation of blood pressure are carried out both through the vagus and sympathetic nerves. Following paralysis or section of the vagi, Hering (1924) produced a fall in blood pressure without inhibition of the cardiac rhythm in dogs. He also pointed out that stimulation of the right carotid sinus elicits a greater fall in blood pressure than equal stimulation of the left, and advanced the opinion that, of the reflexes arising in the carotid sinus, those

which affect the blood vessels directly play a greater role in the regulation of blood pressure than those which act upon the heart, but the fall in blood pressure due to the latter reflexes takes place more rapidly than that due to the former Occlusion of the common carotid artery by external pressure, according to Hering (1927) results in a rise of blood pressure by setting up pressor reflexes from the collapsed carotid sinus This rise is diminished following bilateral section of the splanchnic nerves (Kremer and Wright, 1932) and usually is abolished by denervation of the carotid sinus (Gemmill, Overstreet and Hellman, 1933) Hering's findings, like those of Heymans (1929), show clearly that cerebral anemia produces its effects on blood pressure not only by decreasing the oxygen tension and raising the carbon dioxide tension in the vasomotor center but also through reflexes initiated in the carotid sinus

Almost continuous conduction of afferent impulses arising in the carotid sinus under physiological conditions, into the medulla oblongata via the carotid sinus nerve has been demonstrated by Bronk (1931) According to his findings, a burst of impulses followed by an interval of comparative inactivity accompanies every heart cycle The discharge is coincident with the rapid rise in arterial pressure revealed by the curve of the carotid pulse Following this rapid discharge, there are scattered impulses throughout diastole When the blood pressure is high, the discharge becomes continuous, a phenomenon which also accompanies asphyxia The discharge in the carotid sinus nerve, according to Bronk, in general is similar to that in the depressor nerve On the basis of his findings, the activity of the receptive endings in the arch of the aorta and the carotid sinus appears to be a function both of the absolute level of pressure and the rate of pressure change

In a study of afferent impulses from single end organs in the carotid sinus in the rabbit, Bronk and Stella (1932) demonstrated that with the beginning of the rapid rise in pressure during systole the end organ starts to discharge impulses at a rate of about 55 per second, the rate then decreases as the pressure falls The duration of this discharge seems to be a function of the threshold of the end organ, the mean blood pressure and the form of the pulse curve At low or medium pressure, the discharge sometimes ceases during diastole, although a second volley of impulses may occur, particularly when the pulse curve is dicrotic In experiments carried out with the mean blood pressure ranging from about 40 mm Hg to 150 mm Hg, single end organs sometimes did not discharge at all or but a few times during systole As the mean blood pressure increased, the impulses became more frequent during systole and the discharge of longer duration until, with high blood pressure, they became continuous with only slight variations in frequency corresponding to systole and diastole Starting with a subthreshold pressure at which no endings are stimulated, in preparations in which several nerve fibers are intact, they found that first one and then another end organ is stimulated during systole as their several thresholds are reached It may be assumed, therefore, that more and more impulses reach the corresponding centers in the medulla oblongata from the carotid sinus, in the normal animal, as the blood pressure rises, due to an increasing number of end organs which become functionally active and a higher frequency and longer duration of discharge from the several end organs

Heymans (1929) devised an experimental method by which the circulating blood of one dog could be passed through the blood vessels of the isolated head of another dog or through its isolated carotid sinuses and the reflex effects on the heart rate and blood pressure of the body of the latter dog, brought about through the intact vagus nerves, could be recorded. The body of the dog with the isolated head remained connected with the latter only by means of the intact vagus nerves and it was kept alive during the experiment by means of artificial respiration. The results of the experiments in which the strange blood was passed through the vessels of the isolated head show clearly that hypertension in the cerebral vessels elicits cardiac inhibition, and hypotension in the cerebral vessels results in cardiac acceleration. The results of the experiments in which the strange blood was passed through the isolated carotid sinuses were essentially similar to those brought about by passing it through the entire cerebral circulation, but the same reflexes were not elicited when the strange blood was passed through the vessels of the isolated head following section of the carotid sinus nerves. On the basis of these results, the conclusion was drawn that the reflex effects of the cerebral circulation on cardiac rhythm are brought about through carotid sinus reflexes and that the receptors in the wall of the carotid sinus respond to chemical stimuli as well as to distention of the vessel. Robb and Weiss (1933) also reported certain experimental data which they interpreted as supporting the hypothesis that the receptors in the carotid sinus may be stimulated directly by chemical substances in the circulating blood.

In another series of experiments in which the isolated carotid sinuses were perfused with the circulating blood of another animal, following section of the vagus nerves but with the animal otherwise intact, hypotension in the carotid sinuses resulted in a rise, and hypertension in a fall in blood pressure. The fall in blood pressure in this instance was not accompanied by cardiac inhibition.

The results of experiments reported by Heymans (1929) and Goormaghtigh and Elaut (1929) support the assumption that the regulation of adrenin secretion which is associated with the regulation of the normal resting blood pressure is accomplished reflexly through the aortic and carotid sinus nerves. When the carotid sinuses are denervated but the aortic nerves are intact, changes in the general blood pressure still reflexly modify adrenin secretion but produce no effect on the output of adrenin when the aortic nerves also are cut.

Although the regulatory influence of the depressor and carotid sinus nerves on blood pressure is most apparent in the presence of a threatened rise in pressure, they also play an important role in protecting against a fall in blood pressure. According to Kremer and Wright (1932), bilateral section of the splanchnic nerves in cats with the depressor and carotid sinus nerves intact results in comparatively small falls in blood pressure, commonly 0 to 15 per cent and occasionally 25 per cent, although vasodilatation in the splanchnic area is evident. When the aortic and carotid sinus nerves were inactivated, in their experiments, bilateral section of the splanchnic nerves resulted in falls in blood pressure which on the average amounted to 50 per cent. When either the aortic or the carotid sinus nerves were left intact the fall in blood pressure was greatly reduced. A

lesser degree of protection was afforded by one intact carotid sinus nerve but one intact depressor nerve alone was comparatively ineffective

The relatively slight falls in blood pressure reported by Kremer and Wright following section of the splanchnic nerves with the aortic and carotid sinus nerves intact, emphasize the role of compensatory vasoconstriction in other parts of the body, including the skeletal muscles Evidence also is advanced which suggests that the vasoconstrictor control of the vessels of the skeletal muscles is of greater functional significance than usually is conceded

Pressure on the carotid sinus in man as demonstrated by Mandelstamm (1929) by means of electrocardiographic records may reflexly arrest the heart completely Atrio-ventricular conduction also may be interfered with and the heart block may be partial or complete Paroxysmal tachycardia also may be arrested (Danielopolu, 1929) but as a rule only for a short time

In certain individuals, the carotid sinus appears to be hyperexcitable and reflex effects may be elicited with extraordinary ease In a case reported by Roskam (1930), the slightest pressure on the skin over the sinus might produce complete arrest of the heart for as long as fifteen seconds and, consequently, epileptiform convulsions Investigation of this case showed that the heart stopped only from pressure on the common carotid artery or adjacent structures Hypersensitivity of the afferent nerve endings in the carotid sinus as suggested by Roskam, may be a factor in certain types of syncope or epileptiform convulsions

Like Hering and Heymans not a few other investigators on the basis of their experimental findings have supported the theory that the regulatory influence of the impulses arising in the carotid sinuses on cardiac rhythm and blood pressure is exerted through reflex mechanisms and not through centers of a higher order in the brain stem Hering (1930) advanced the hypothesis that the depressor and carotid sinus nerves constitute the afferent limbs of an autoregulatory reflex system which tends to check both high and low blood pressure by maintaining a functional balance between the cardiac accelerator and vasoconstrictor nerves on the one hand and the cardiac inhibitory and vasodilator nerves on the other Any marked deviation from normal blood pressure according to this hypothesis, must be regarded as the result of a functional disturbance of this autoregulatory mechanism

According to Koch (1931), the carotid sinus nerves exercise solely a tonic inhibitory influence on the circulation He regards acceleration of the heart and rise in blood pressure on occlusion of the carotid sinuses as due to a decrease or abolition of the inhibitory action due to a fall in pressure in the carotid sinuses below threshold value This view is supported by the fact that section of the carotid sinus nerves or cocainization of the carotid sinuses produces similar pressor effects Although the reflexes initiated in the carotid sinus are mainly depressor, the existence of pressor fibers in the carotid sinus nerves is not precluded

Contrary to the view that the regulatory control of cardiac rhythm and blood pressure is carried out solely through reflex mechanisms the results of Wright's (1930) studies of the action of ergotamine on vasomotor reflexes seem to indicate that the regulation of blood pressure, at least under certain conditions, involves central mechanisms of a higher order

Ergotamine in small doses, in his experiments on cats prolonged the latent period of the depressor reflex, decreased the rate and extent of the fall in blood pressure and finally abolished the reflex completely In larger doses, it also prolonged the latent period of the pressor reflex decreased the rate and extent of the rise in blood pressure, and finally abolished this reflex at a stage in which the vasomotor center still responded strikingly to acute anemia These results, which indicate that the effect of ergotamine is exerted on the afferent side of the vasomotor center, militate against the assumption that the regulation of the cardiac rhythm and blood pressure is mediated solely through direct reflex mechanisms Certain observations reported by Cromer and Ivy (1931) also tend to show that the carotid sinus mechanism is not indispensable in the regulation of cardiac rhythm and blood pressure In a study of the effects of exercise on the heart rate blood pressure and respiration in dogs, they obtained results following section of the carotid sinus nerves which differed but slightly from the results obtained with the carotid sinus mechanisms intact On the basis of these results, they concluded that "the physiological role of the carotid sinus as a reflexogenic center for controlling blood pressure heart rate and respiration is readily taken over by other mechanisms in the dogs" Raab (1932) also advanced certain data which seem to indicate that the vasomotor center is stimulated directly by a decrease in the blood pressure in the cerebral vessels

In view of the increasing volume of data which fail to support the hypothesis that the blood pressure and the heart-rate are regulated mainly through the carotid sinus mechanism, particularly those data which seem to support the assumption that the vasomotor center is stimulated directly by changes in the cerebral blood pressure Bouckaert and Heymans (1933) carried out experiments on dogs designed to test this assumption According to their findings the low blood pressure and the reduction in the volume of blood flowing through the cerebral vessels brought about by occlusion of the common carotid arteries, their efferent branches, or the vertebral arteries do not directly stimulate the vasoconstrictor center Low pressure in the carotid sinus, however results in stimulation of the vasoconstrictor center via the carotid sinus nerve, although it also results in reflexly increasing the cerebral blood pressure and the volume of blood flowing through the cerebral vessels Conversely, high pressure in the carotid sinus results in depression of the vasoconstrictor center via the carotid sinus nerve, although it also results in reflexly diminishing the cerebral blood pressure and blood supply On the basis of these findings they have concluded that the vasoconstrictor center is not directly sensitive to changes in cerebral blood pressure and blood volume unless these are very extreme The tonus of the vasoconstrictor center is maintained chiefly by the arterial CO_2 tension, but normally is inhibited by the effects of the normal blood pressure exerted through the aortic and carotid sinus nerves consequently, these nerves play a dominant role in the regulation of the blood pressure

When tissues or organs are in a condition of high activity, their nutritional and respiratory requirements are increased and their blood vessels are dilated mainly through local, direct and reflex effects of temperature and metabolites Experimental data advanced by Rein (1931) and Bouckaert and Heymans (1935) indicate that the blood vessels of tissues or

organs in states of nutritional vasodilatation are temporarily irresponsive either to nervous or hormonal vasoconstrictor influences exerted through the pressoreceptive reflex mechanisms involved in blood pressure regulation The principal vasoconstrictor effect frequently the only one, is exerted on the vessels of resting organs or tissues, consequently, blood is shifted readily from tissues whose respiratory and nutritional needs are slight for the time being to tissues whose needs are greater, although the general blood pressure is maintained at normal levels or regulated at levels above normal

The cerebral vessels, according to Bouckaert and Heymans (1935), do not participate actively in the pressoreceptive regulation of the general blood pressure but always behave like the vessels of an organ in which the nutritional requirements are elevated Thus whenever the necessity arises, blood may be shifted from other organs in a state of metabolic rest to the cerebral circulation During periods of hypotension blood is diverted from the peripheral and splanchnic areas toward the cerebral circulation, due to pressoreceptive reflex activity initiated particularly in the carotid sinuses During periods of hypertension, some blood is diverted from the brain due to the activity of the same reflex mechanisms The peripheral cephalic tissues and the thyroid gland play a significant rôle in these reactions As demonstrated by Rein *et al* (1932), increased pressure in the carotid sinus elicits reflex thyroid vasodilatation, thus diverting a certain amount of blood from the carotid arteries through the thyroid gland It also elicits vasodilatation in the peripheral cephalic tissues Lowering of the pressure in the carotid sinus results in the opposite reactions The extracranial circulation, consequently, plays a leading part in the regulation of cerebral circulation particularly in emergencies (Heymans, 1938)

The significance of these findings regarding the behavior of the cerebral blood vessels is emphasized by the results of an extensive series of studies on the vasomotor control of the cerebral vessels summarized by Forbes and Cobb (1938) The results of these studies, carried out by the above investigators and their collaborators, show clearly that the cerebral vessels are supplied both with vasoconstrictor and vasodilator nerve fibers Vasoconstrictor fibers are distributed unequally to the vessels in the various parts of the brain and probably do not reach the smallest arteries and arterioles Direct stimulation of the vasoconstrictors elicits only slight constriction of the cerebral vessels, as compared with the vasoconstrictor response of comparable stimulation observed in other organs The arterioles undergo no appreciable changes in caliber and the flow of blood through the capillaries which, at least in the pia mater, appear to be always open is remarkably steady The vasomotor mechanism obviously is more effective in some parts of the brain than in others and may aid in diverting blood from one region to another It may help arteries to regain normal tonus after extreme dilatation and thus limit undesirable fluctuations but experimental data do not support the assumption that it can cause the arteries to constrict sufficiently to bring about ischemia Chemical agents, particularly CO_2, play a major role in cerebral vasomotor regulation In an experimental study reported by Norcross (1938), CO_2 caused a marked increase in the flow of blood in the cerebral vessels, inhalation of pure oxygen and hyperventilation with pure air caused a marked decrease Administration of adrenin, ephedrin and posterior pituitary extract caused

an increased flow in the brain as a secondary result of a rise in blood pressure

The effect of the vasomotor reflexes initiated in the pressoreceptors in the mesenterico-intestinal zone usually are not markedly manifest but nonetheless important These reflexes probably are involved mainly in the local segmental and regional distribution of blood in the splanchnic and peripheral areas

Upright posture in man not uncommonly results in swelling of the legs and diminished flow of blood through the lower half of the body (Ude, 1934 Youmans Akeroyd and Frank 1935, Grill 1937) At the same time there is a fall in blood pressure which may be accounted for in part by splanchnic vasodilatation This probably is not a major factor since section of the splanchnic nerves in man according to Ghrist (1930) and Roth (1937) does not materially alter the circulatory response to posture These findings suggest that imperfect circulatory compensation in man in the upright position is due to stagnation of blood in the lower extremities rather than in the splanchnic area In an experimental study of the compensatory mechanism of the splanchnic circulation during changes in posture in animals Edholm (1942) found that the fall in blood pressure in the cat when the trunk is in the vertical position with the hind feet down is due to the collection of blood not in the splanchnic area but in the liver The compensation following this fall is due in part to the reaction of the splanchnic vessels The recovery of blood pressure on restoring the animal to the horizontal position is due to the return to the right atrium of blood accumulated in the liver

Capillary Regulation —Capillary contraction elicited by reflex and direct nerve stimulation has been reported by various investigators Steinach and Kahn (1903) who first reported contraction of capillaries in response to sympathetic stimulation observed it in the nictitating membrane of the frog Krogh Harrop and Rehberg (1922) reported contraction of the capillaries in the web of the frog's foot elicited by electrical stimulation of the lower portion of the sympathetic trunk In these instances the latent period was so long that the capillary response could have been regarded as secondary to contraction of the arterioles

The results of investigations of the causes of caliber changes in capillaries have led to widely divergent conclusions On the basis of independent studies Jacobj (1920) Marchand (1923), Rehberg and Karrier (1923) and Nesterow (1925) supported the theory that changes in the caliber of the capillaries in general are secondary to changes in the caliber of the arteries especially their terminal branches including the arterioles On the other hand Pribram (1920) Mertz (1920), Nickau (1920–1921), Parrisius (1921) Kylin (1922) Jurgensen (1923) Hagen (1923), and Bensley and Vimtrup (1928) have supported the theory that the capillary walls contain contractile elements and that these vessels undergo changes in caliber in response to nerve impulses These changes according to Hyndman and Wolkin (1941), include active capillary dilatation They have advanced experimental data in support of the assumption that, in man the cutaneous capillaries are supplied with sympathetic dilator fibers which constitute part of the general vasodilator mechanism A third group of investigators including Kukulka (1920), Moog and Ambrosius (1922) and Redisch (1923),

have supported the theory that chemical stimuli constitute a major factor in the causation of caliber changes in the capillaries

Krogh (1927) maintained that the capillaries, like the arteries, are influenced reflexly in many ways and that the reflexes involved are carried out through sympathetic fibers He failed to produce caliber changes in peripheral capillaries by stimulation of the distal ends of dorsal spinal nerve roots but regards localized hyperemia, due to stimulation of the skin, as the result of axon reflexes carried out through collaterals of the sensory fibers which mediate cutaneous pain These axon reflexes according to Krogh, bring about active dilatation of many of the capillaries in the cutaneous area involved

The solution of the problems involved in caliber changes in capillaries is beset with inherent difficulties due to the marked hydrostatic effect on these vessels of any changes in the caliber of the arterioles In most instances in which capillary contractions in response to nerve stimulation has been observed the latent period has been relatively long and the mechanism involved could not be clearly determined Swelling of endothelial nuclei into the lumen, thus limiting or completely stopping the flow of blood, has been observed by Kahn and Pollack (1931) in the nictitating membrane by Field (1935) in the mesentery of the rat and by Beecher (1936) in the rabbit s ear Beecher observed both swelling of endothelial cells and contraction of Rouget cells According to his observations the latent period may be of the order of one second or longer In a study of capillary reactions in the rabbit s ear with the aid of a transparent chamber Sanders, Ebert and Florey (1940) observed contraction of capillaries in response to cervical sympathetic stimulation and a marked increase in the flow of blood through the capillaries following section of the cervical sympathetic trunk The mechanism by which the capillary lumen is occluded in response to nerve stimulation involved swelling of an endothelial cell in the region of the nucleus sufficient to occlude the lumen The outside diameter of the capillary was not sensibly diminished and no changes were observed in the Rouget cells in the field of observation The latent period from the beginning of stimulation was fifteen to twenty seconds and the capillary remained contracted up to forty-five seconds after cessation of stimulation

Certain investigators including Hoffmann and Magnus-Alsleben (1922), Wessley (1924) and Watanabe (1938) have maintained that capillary permeability is increased following sympathetic denervation Rous, Gelding and Smith (1931) observed that vital dyes circulating in the blood pass through the normally innervated capillary walls more rapidly toward the venous than toward the arterial end The capillaries, therefore exhibit an increasing gradient of permeability from the arterial toward the venous end This gradient according to Hesselman (1932), disappears following sympathetic denervation His findings seem to indicate that the increased capillary permeability following sympathetic denervation is brought about by removal of the permeability gradient and does not depend entirely on capillary dilatation

Experimental data reported by Engel (1941) seem to be somewhat at variance with those cited above This lack of agreement may be correlated with the methods employed In Engel s experiments dye was perfused in the knee joints of cats dogs and rabbits which had been sympathectomized on one side and the local blood flow measured thermo-electrically In the

majority of both acute and long term experiments excretion of the d... was apparently reduced on the sympathectomized side in spite of mark... dilatation of the denervated capillaries. Engel has attempted to expla... this result by postulating a permeability factor which is influenced b... sympathetic nerve impulses. He has advanced the opinion that the effec... of vasomotor changes might be counteracted or balanced by such a facto...

Vascular Reaction Patterns.—The peripheral blood flow, particularly in the extremities, fluctuates continually within relatively wide limits. Some of these fluctuations probably represent rhythmic changes in the vascular tonus. Others are due to various causes including psychic factors.

Burton (1939) has adapted a simple plethysmographic method of recording the volume pulsations of the finger to measurement of instantaneous values of the blood flow of the finger in cc per min per 100 cc of tissue. As indicated by such measurements, the blood flow in the fingers varies from 0.5 to 1 cc to 80 to 90 cc per min per 100 cc of tissue. These minimum and maximum values are subject to change upon slow adaptation to low or high environmental temperatures. The wide range of flow, made possible by the arteriovenous anastomoses, represents not a r... bolic requirement of the tissues but a mechanism for the regulatio... body temperature.

The magnitude of the volume pulse in the finger is closely correl... with volume flow of blood through the tissues; consequently, the met... is useful in studying the fluctuations in the blood flow which occur fr... moment to moment. These fluctuations are rhythmic in nature a... exhibit two main components, a respiratory wave of small amplitude a... slower periodic constrictions of larger amplitude. These reactions occ... simultaneously in the digits of all the extremities; consequently, they mus... be mediated through the vasomotor nerves and represent widesprea... responses through the peripheral sympathetic nerves. Constrictions elic... ited by pain, startle or emotional excitation may also be present and represent a third component in the vascular fluctuations. The amplitude of the volume pulse waves is greatest in the middle range of blood flow and of temperature. It is reduced somewhat during intervals of peripheral vasodilatation and more markedly during intervals of peripheral vasoconstriction. The rhythm also varies in frequency. In general the higher frequencies are associated with cooler conditions and consequent lower average values of the blood flow.

The reactions of the peripheral vessels in the digits and other cutaneous areas have been studied extensively by Hertzman and Dillon with the aid of the photoelectric plethysmograph. According to their findings, spontaneous fluctuations may appear either as constriction or dilatations. They commonly appear as constrictions in the extremities, as dilatations in the skin of the head and of varied character in the ear and nasal septum. They may or may not exhibit synchronism in the different vascular areas. Most of these waves seem to be related to vasomotor activity but some probably represent activity of the vascular musculature which is independent of nerve impulses. Various means of stimulation including auditory and psychic stimuli, cold applications, deep breath and breath holding elicit marked vasoconstrictor reactions in the digits, the skin of the hands and feet and the nasal septum but variable reactions in the skin of the head and ears (Hertzman and Dillon, 1939).

Large and small arteries do not react equally to vasomotor stimuli. The

cutaneous arteries in the fingers, for example, may constrict strongly, as indicated by the volume pulse wave recorded in the pad of the distal segment, while the volume pulse wave record of the radial artery shows no appreciable change (Hertzman and Dillon, 1940) In a more specific study of the relative responses of the dorsal metacarpal, digital and terminal cutaneous arteries of the hand in vasoconstrictor reflexes Hertzman (1941) found that the dorsal metacarpal and digital arteries usually do not participate in the spontaneous fluctuations or in the vasomotor reflexes elicited by loud noises, immersion of the contralateral hand in ice water or application of cold to the finger in the pad of which the volume pulse wave is being recorded A high degree of selectivity in the vasomotor apparatus therefore is indicated

The normal volume pulse wave of the finger pad is essentially similar in contour to the normal volume pulse wave of the radial artery (Dillon and Hertzman, 1941) In patients with arteriosclerosis or hypertension, the digital pulse is altered earlier and to a greater extent than the radial pulse but, because of discrepancies in the alterations which take place in the waves it is impossible to predict from the contour of the radial volume pulse wave what the contour of the digital volume pulse wave will be It is impossible likewise by study of the contours of the digital volume pulse waves to differentiate arteriosclerotic changes in the digital vessel walls from those produced by hypertension particularly if the hypertension is of long standing The contour of the digital volume pulse wave, nevertheless, may afford significant information regarding early changes in the elasticity of the arterial system

The elastic reservoir action of the arterial system has long been recognized The data advanced by Dillon and Hertzman seem to support the suggestion of Greven and Lederschmidt (1939) that there may be a central and a peripheral elastic reservoir, the latter with respect to the hand, beginning somewhere peripheral to the radial artery Data reported by Matthes Gross and Gopfert (1939) also support this suggestion Strict anatomical delimination of the peripheral reservoir must await further study

In an experimental study of vascular reactions to local cooling, Hertzman and Roth (1942) found that when a single finger is immersed in cold water the initial immediate vasoconstriction is due to vasoconstrictor reflexes, as is indicated by the simultaneous vasoconstriction which occurs in the other fingers of the same hand and the opposite hand The reactive vasodilatation which takes place in a chilled finger three to eight minutes after the application of cold is independent of the vasomotor nerves This is evidenced by the facts that the reactive vasodilatation may be limited to the chilled finger and that it may occur while the vasomotor tonus is high in the control fingers In some instances vasoconstriction could be elicited in the chilled finger while the reactive vasodilatation was going on The digital artery does not participate either in the vasoconstrictor reflexes elicited by local chilling or the reactive vasodilatation which follows Its late constriction during continued chilling of the finger seems to be due to the direct effect of reduction in temperature on the artery Certain cutaneous areas seem to be devoid of vasoconstrictor reflex mechanisms Chilling of the skin of the forehead for example, results in gradual vasoconstriction as the temperature falls, which is not followed by reactive vasodilatation The vascular reaction to chilling in this area is comparable to that of a finger of a sympathectomized hand

CHAPTER IX

INNERVATION OF THE RESPIRATORY SYSTEM

Extrinsic Nerves of the Respiratory Tract —The respiratory tract, including the nasal mucosa, larynx, trachea, bronchi and lungs, is innervated through sympathetic and parasympathetic nerves Associated with these nerves are afferent fibers of spinal ganglion origin and afferent components of the vagi The afferent innervation of the nasal mucosa is derived mainly from the trigeminal nerves and the nervi intermedii The sympathetic innervation of the nasal mucosa is derived mainly from the superior cervical ganglion via the internal carotid plexus, its parasympathetic innervation mainly from the sphenopalatine ganglion The voluntary musculature of the upper portion of the respiratory tract is innervated through the facial glossopharyngeal and vagus nerves The parasympathetic and vagus afferent innervation of the larynx and trachea is supplied mainly through the laryngeal branches of the vagi Their sympathetic supply is derived mainly from the superior cervical sympathetic ganglia through the pharyngeal plexus and the sympathetic rami which join the vagi The bronchi and lungs are supplied mainly through the pulmonary plexuses which are made up of vagus and sympathetic components plus the neurons in the pulmonary ganglia (Fig 16)

The superior laryngeal nerve is a branch of the vagus which receives its efferent fibers from the accessory nerve It passes downward and medialward toward the thyroid cartilage and ends by dividing into a large internal and a small external laryngeal branch It is joined by rami from the pharyngeal plexus and the sympathetic The internal laryngeal branch supplies the mucous membrane of the pharynx reaching upward to the epiglottis and the base of the tongue It communicates inferiorly, beneath the lamina of the thyroid cartilage, with the inferior laryngeal nerve The external branch supplies the cricothyroid muscle All the other muscles of the larynx derive their motor nerve supply from the inferior laryngeal nerve which is a terminal branch of the recurrent The latter nerve also supplies branches to the trachea and not uncommonly is joined by a ramus from the middle cervical sympathetic ganglion According to Tschelustkin s (1927) findings in the dog the nerves which approach the trachea and bronchi give rise to a loose-meshed plexus in the connective tissue along the ventral and lateral aspects of these organs and another along their dorsal aspect Minute ganglia occur sparsely scattered in the former plexus The latter contains a large number of ganglia of various sizes and forms These plexuses are continuous with the pulmonary plexuses

As the vagus nerve on either side reaches the dorsal aspect of the root of the lung in man, it breaks up into numerous branches which become incorporated in the posterior pulmonary plexus Some fibers from both vagi pass over the upper border of the root of the lung and enter the much smaller anterior pulmonary plexus These plexuses are intimately connected with each other and with the cardiac plexuses

The anterior pulmonary plexus lies in contact with the root of the lung anteriorly It is joined on both sides by a few fibers from the corresponding

part of the deep cardiac plexus and on the left side also by fibers from the superficial cardiac plexus It supplies structures in the anterior part of the root of the lung

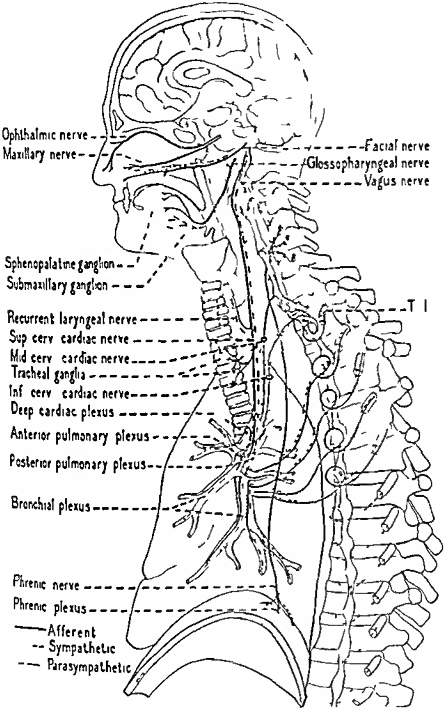


FIG 46 —Diagrammatic illustration of the sympathetic parasympathetic and afferent innervation of the respiratory tract

The posterior pulmonary plexus lies behind the root of the lung It is made up mainly of branches of the vagus and slender rami from the second, third and fourth thoracic sympathetic ganglia This plexus gives rise to numerous branches which form delicate plexuses on the bronchi and vessels as they enter the substance of the lung

Intrinsic Nerves of the Respiratory Tract —The nerves in the walls of the respiratory tract include large and small myelinated and unmyelinated

fibers and numerous ganglia Some of the latter comprise but few ganglion cells, others many These ganglion cells are similar to those in the cardiac and enteric plexuses They are to be regarded as parasympathetic and constitute the ganglionic components of vagus efferent chains Ganglia occur in the walls of the larynx, epiglottis trachea and bronchi but are most numerous in the posterior wall of the trachea (Polschko, 1897) Larsell and Dow (1933) observed ganglion cells as far distalward as the proximal ends of the bronchi of the third order Okamura (1937) reported the occurrence of ganglion cells as far distalward as the alveolar ducts in the lung of the cat In general, the larger fiber bundles in the walls of the respiratory passages run longitudinally but branch and anastomose freely to form plexuses In the larynx, there is a subepithelial and a deep plexus the latter alone containing ganglia In the epiglottis, Polschko recognized only a subepithelial plexus Both the subepithelial and deep plexuses are present in the walls of the trachea and larger bronchi In the walls of the smaller bronchi, the two plexuses blend into one This plexus can be traced as far as the respiratory bronchioles, but nerve fibers running either singly or in small bundles continue still farther into the walls of the atria Afferent fibers extend distalward as far as the proximal ends of the alveolar ducts (Larsell and Dow, 1933)

The bronchial plexuses are continuous with the tracheal plexuses but are made up mainly of fibers derived from the anterior and posterior pulmonary plexuses According to Larsell (1922), the nerves which enter the lungs from the latter plexuses are distributed to the bronchi, blood vessels and visceral pleuræ Perhaps most of the fibers enter the bronchial plexuses The subepithelial plexus is located mainly between the cartilaginous plates and the bronchial musculature, the deep plexus is located between the cartilaginous plates and the parenchyma of the lung The intrapulmonary ganglia are located chiefly in the latter plexus and usually occur at the bifurcations of the bronchi and at the points of junction of the larger fiber bundles in the plexus

The plexuses include both myelinated and unmyelinated fibers Many of the larger myelinated fibers can be traced to sensory terminations in the epithelium and the subepithelial tissue as far distalward as the bronchioles and atria These are general visceral afferent fibers mainly of vagus origin Other myelinated fibers terminate in the intrinsic ganglia in pericellular networks These are preganglionic fibers of vagus origin Following unilateral vagotomy in the rabbit, Larsell and Mason (1921) found that nearly all the pericellular networks in the intrapulmonary ganglia of the homolateral side underwent degeneration They concluded that the few which remained intact represent the terminations of preganglionic vagus fibers from the contralateral side There is no evidence that preganglionic fibers of spinal origin terminate in the ganglia in the walls of the respiratory tract The smallest myelinated fibers and the unmyelinated ones are mainly of sympathetic origin and axons of the neurons in the intrinsic ganglia They are the postganglionic fibers which supply the musculature and glands of the respiratory tract The mucous glands receive fibers mainly from the subepithelial plexus

Nerve Terminations in the Respiratory Tract — Sensory — Polschko (1897), using the methylene blue technic described three types of sensory fiber terminations in the larynx and epiglottis end arborizations and end

bulbs or knobs located in the subepithelial tissue and branched endings which ramify in the epithelium These terminal structures are connected with relatively large myelinated fibers which may be regarded as fibers of cerebrospinal origin

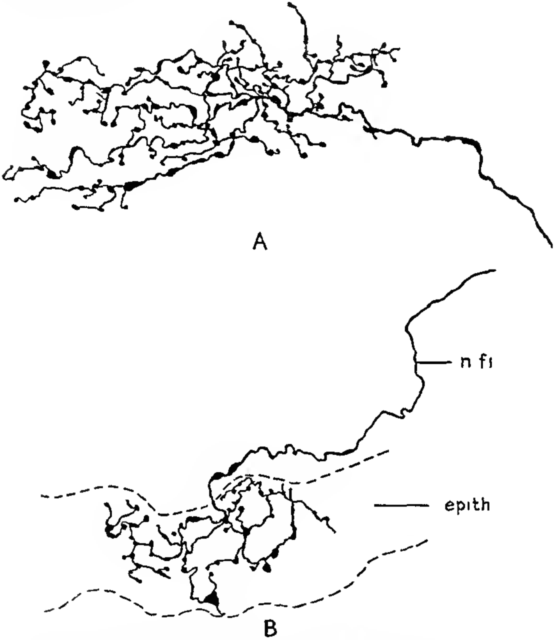


FIG 47 — A Sensory nerve termination in the epithelium of a primary bronchus within the lung in the rabbit B Sensory nerve termination at the point of division of one of the larger bronchi in the rabbit (Larsell)

Larsell (1921) using the methylene blue technic on the rabbit s lungs found sensory nerve endings in the epithelium of the primary bronchi at the points of origin of the bronchi of the various orders and in the walls of the atria The sensory nerve terminations in the epithelium of the primary bronchi are highly complex Relatively large myelinated fibers deviate from the fiber bundles in the plexiform meshworks around the bronchi and approach the bronchial epithelium either singly or in bundles of two or three fibers Individual fibers penetrate the epithelium and terminate

in the dog including flattened receptors along the alveolar ducts complex branching ones in nodules in the walls of the air sacs and more delicate ones with straight and coiled terminal branches in the alveolar walls

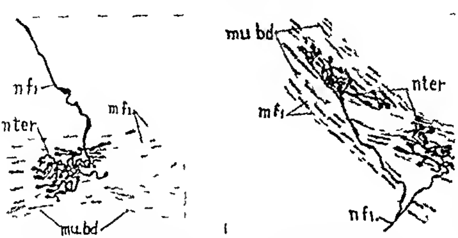


Fig 50 —Smooth muscle spindles in bronchial musculature child aged eight months Intra vitam methylene and borax carmine (Larsell and Dow)

Motor —The musculature of the larynx trachea and bronchi is richly supplied with efferent nerve fibers of small caliber which are either unmyelinated or invested with a very thin myelin sheath Many of these can be traced directly from neurons in the intrinsic ganglia, others merely traverse these ganglia on the way to their peripheral distribution The latter are postganglionic fibers which have their origin in ganglia of the *sympathetic trunk*

In the larger bronchi, the bundles of nerve fibers in general run parallel to the smooth muscle bands At intervals nerve fibers deviate from these bundles either singly or in small strands and penetrate the muscle On reaching the muscle the individual nerve fibers give rise to numerous slender branches which run between the muscle fibers and at intervals give off short twigs which terminate near the nuclei of the smooth muscle cells Nerve bundles constantly diminishing in size may be traced as far as the bronchioles and alveolar ducts From these bundles fibers may be traced into the musculature of the bronchioles and the sphincter-like bands at the openings of the alveolar ducts into the atria Efferent nerve fibers also terminate in relation to the bronchial glands

Innervation of the Pulmonary Vessels —The pulmonary artery and its branches are more richly supplied with nerves than the usual anatomical descriptions and the results of physiological experimentation seem to indicate but less richly than the bronchial arteries In the rabbit, according to Larsell (1921), relatively large nerve trunks become associated, near the hilum of the lung, with the larger branches of the pulmonary artery These nerves wind about the blood vessels as they continue distalward and at irregular intervals, give off fibers which run roughly parallel to the artery for a short distance and then turn almost at right angles and divide into several main branches one of which usually runs proximalward and another distalward along the artery (Fig 51) These branches in turn give rise to smaller varicose branches which may undergo still further subdivision and finally penetrate the media to terminate in relation to the

smooth muscle cells. Karsner (1911) described a similar arrangement of nerve fibers in the walls of the pulmonary arteries in the dog. Larsell also observed sensory nerve terminations in the adventitia of the pulmonary arteries in the rabbit. These are connected with relatively large myelinated fibers like those which may be traced to the sensory terminations in the bronchi.

According to Larsell and Dow (1933), the nerve fiber bundles along the branches of pulmonary arteries diminish in size with the arteries. The smaller arteries are accompanied by nerve fiber bundles of minute size. Slender filaments also follow the courses of the capillaries about the alveolar ducts and air sacs, and at intervals give rise to twigs which terminate in relation to the capillary walls. The pulmonary veins have a relatively meager nerve supply but the nerve fibers observed in relation to the media

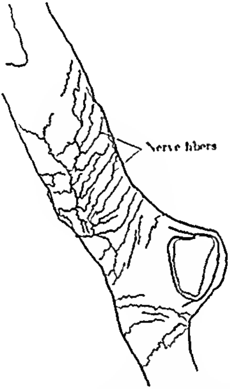


FIG. 51.—Distribution of nerve fibers in the musculature of the pulmonary artery in the rabbit. (Larsell.)

bear the same relation to the musculature as in the pulmonary arteries (Berkeley, 1893; Larsell, 1921).

Both Berkeley (1893) and Larsell (1921) observed that the smaller branches of the pulmonary artery which lie in close proximity to small bronchi receive fibers from the nerve plexus around the latter. Most of the available data, particularly those obtained in experimental studies carried out on mammals, support the view that the major portion of the nerve supply to the pulmonary vessels is sympathetic (Franklin, 1932, Daly, 1933, Elftman, 1943). Afferent nerve fiber terminations in the adventitia of the pulmonary arteries also have been described (Dogiel, 1898, Larsell, 1922, Larsell and Dow, 1933).

Innervation of the Visceral Pleura.—Afferent nerve endings in the visceral pleura have been described by various investigators. In the dog

and the rabbit, according to Larsell (1922), the nerves which supply the visceral pleura emerge from the plexus on the pulmonary arteries near the hilum of the lung, enter the pleura and run for some distance as fairly compact bundles and then break up into smaller ones. The nerve fibers are distributed mainly to the pleura near the margins of the pulmonary lobes particularly on the inner surfaces. In the rabbit, the fiber terminations in the visceral pleura are small and of simple structure, in the dog they are larger and more complex. McLaughlin (1933) described small encapsulated afferent end organs in the visceral pleura of the cat. In the lungs of the pig and man, as reported by Larsell (1935), bundles of nerve fibers approach the visceral pleura *via* the interlobular septa from the perivascular plexuses within the lung. These fibers, like those which reach the visceral pleura in the dog and the rabbit, are derived from the plexus on the pulmonary artery. Some of them end in relatively simple afferent terminal structures in the pleura. The results of degeneration experiments on rabbits reported by Larsell, though not conclusive, strongly suggest that the nerve fibers distributed to the visceral pleura are mainly components of the dorsal roots of the upper thoracic nerves which reach the lung *via* the upper thoracic and inferior cervical sympathetic ganglia.

Pulmonary Reflexes.—Direct Bronchial Reflexes.—Direct reflexes involving the tracheal and bronchial musculature which are initiated by stimulation of afferent nerve fibers which supply the respiratory tract play an important rôle in the respiratory processes. Irritation of any part of the tracheal or bronchial mucosa elicits reflexes which involve the musculature of the respiratory tract either in whole or in part. As pointed out by Larsell (1921), the sensory nerve terminations situated at the openings into the respiratory portion of the lung differ somewhat morphologically from those situated in the mucosa of the larger bronchi. Whether or not these sensory terminations differ functionally is problematical. It seems not improbable, as has been suggested by Larsell, that the afferent terminations in the larger bronchi represent a type of tactile terminations which is stimulated by masses of mucus or foreign particles within the bronchi. The reflex contraction of the bronchial musculature elicited by such stimulation would tend to prevent the displacement of matter in the respiratory passages distalward. The sensory terminations situated at the openings of the respiratory portion of the lungs might conceivably also serve the purpose of guarding against the entrance of foreign matter into the atria and air sacs by eliciting reflex constriction of the muscle bands at the openings of the alveolar ducts into the atria, but, as Larsell suggested, they seem to be better adapted, due to their structure, to react to pressure stimuli than to touch. Although they may mediate impulses which elicit direct bronchial reflexes, they probably are stimulated by partial collapse of the lungs at each expiration and mediate impulses which are involved in the reflex control of respiratory rhythm. If the sensory terminations located in the walls of the atria are stimulated by changes in the CO_2 tension of the air in the atria and air sacs, as has been suggested by Larsell and Dow (1933), they also play a role in the reflex control of the respiratory rhythm.

The visceral pleura quite generally has been regarded as insensitive to stimulation (Capps, 1911; Hoffmann, 1920). Larsell (1928) elicited respiratory reflexes in decerebrated dogs by inflating a small rubber bal-

loon placed between the lobes of the lung These reflexes involved inhibition of the inspiratory movement and initiation of the expiratory blast On the basis of his results he concluded that the nerve endings in the visceral pleura on the interlobar surfaces of the lung were stimulated by mechanical contact He also expressed the opinion "that the nerve endings in the pleura are normally stimulated by the contact of adjoining interlobar surfaces during extreme inflation of the lung, although such stimulation probably occurs but rarely, if ever in normal respiration with intact vagus nerves "

Bronchoconstrictor Fibers —Due to the elasticity of the cartilage rings in the trachea and larger bronchi these tubes tend to assume a maximum diameter, but the tonus of the tracheal and bronchial muscles normally imposes on these cartilage rings a certain degree of tension This tonus, as indicated by the results of physiological experimentation, is mediated through the parasympathetic nerves Section of the vagi results in dilatation of both the trachea (Einthoven 1892) and bronchi (Weber 1914) Stimulation of the peripheral end of the vagus if the nerve is cut proximal to the origin of its recurrent branch elicits diminution in the caliber of both the trachea and the bronchi When either vagus nerve is stimulated in this manner, diminution in the caliber of the bronchi is most marked on the homolateral side, but is also apparent on the contralateral side This result indicates that some vagus fibers normally cross over and enter the pulmonary plexus on the opposite side In the cat the extent of the crossing varies widely In some animals practically all the vagus fibers supplying the bronchioles are derived from the opposite side, in others, nearly all of these fibers are derived from the same side Crossing of a certain percentage of the bronchoconstrictor fibers seems to be the rule rather than the exception (Dixon and Ransom 1912)

Powerful excitation of the cervical sympathetic in the cat according to Dixon and Ransom, sometimes results in bronchoconstriction Conversely, vagus stimulation occasionally elicits bronchodilatation In experiments reported by Hebb (1940) the most frequent response of the bronchial musculature in the isolated perfused lung of the guinea-pig to sympathetic stimulation was marked contraction Bronchodilatation occurred occasionally under special conditions The bronchoconstrictor response was quantitatively comparable to that resulting from the injection of acetylcholine The sympathetic innervation of the bronchial musculature obviously includes some cholinergic fibers at least in some animals

Bronchodilator Fibers —The bronchodilator fibers are sympathetic and arise mainly in the inferior cervical and upper thoracic ganglia The preganglionic fibers involved are components of the upper three thoracic nerves Stimulation of the thoracic end of the cut cervical sympathetic trunk commonly results in bronchodilatation on one or both sides The reaction is more marked, however, when the stimulus is applied to the upper thoracic rami The bronchodilator fibers also have a bilateral distribution In some cases according to Dixon and Ransom, the sympathetic supply to the bronchioles is derived almost entirely from the opposite side, in others, the crossing of these fibers is less complete The crossing of a certain percentage of the sympathetic fibers supplying the bronchi seems to be the rule rather than the exception These findings of Dixon and Ransom have been corroborated by the findings of Le Blanc and

van Wijngaarden (1924). The rhythmic changes in the caliber of the bronchi during respiration probably are essentially passive (Ellis, 1936).

Afferent Stimulation and Bronchomotor Reflexes.—Bronchoconstriction may be elicited reflexly by a variety of afferent stimuli, *e. g.*, irritation of the mucous membrane of the nose and larynx and afferent stimulation of various nerves. Dixon and Ransom (1912) elicited bronchoconstriction by stimulation of the central end of one vagus nerve while the other remained intact, and by stimulation of the central ends of the thoracic sympathetics, the central ends of the central ends of the thoracic the inferior cervical ganglion and the central ends of the accelerator nerves connected with rami of the second and third thoracic nerves. In no case did they observe bronchoconstriction after section of both vagi.

Bronchodilator reflexes are readily elicited by stimulation of the central end of one or both vagus nerves when both are severed. These reflexes are not abolished by section of the cervical sympathetic trunks but are abolished by section of the spinal cord in the upper cervical region or section of the bronchial nerves arising from the inferior cervical and upper thoracic ganglia. They obviously are mediated through a center in the medulla oblongata and are carried out through the white rami of the first, second and third thoracic nerves (Dixon and Ransom, 1912).

Bronchomotor Responses to Sympathomimetic and Parasympathomimetic Substances.—The relief of bronchospasm by the administration of adrenin in patients suffering from bronchial asthma is a common clinical observation. Januschke and Pollock (1909) showed that adrenin causes slight dilatation of the bronchioles in both decerebrated and ether anesthetized cats but if by the use of a drug, *e. g.*, muscarine, the bronchioles are first thrown into a condition of tonus adrenin produces profound bronchodilatation. Trendelenburg (1912) also found that adrenin caused marked relaxation of the muscle in an isolated ring of a bronchus. In experiments on cats Dixon and Ransom found that whenever the bronchioles are not fully relaxed adrenin causes a maximal active bronchodilatation. Atropine brings about a passive bronchodilatation due to its paralytic action on the parasympathetic terminations. Acetylcholine commonly causes bronchoconstriction. In Hebb's (1940) experiments bronchoconstriction elicited either by nerve stimulation or by the administration of acetylcholine was suppressed by adrenin, ergotoxine or atropine in appropriate doses.

Vasomotor Control of the Pulmonary Vessels.—The pulmonary vessels as stated above are supplied with nerve fibers both through the sympathetic and the parasympathetic nerves. The data bearing on the physiologic actions of these nerves respectively in the regulation of the pulmonary circulation are not in complete agreement. Henriques (1892), Bradford and Dean (1894), François-Franck (1895) and Plumier (1904) advanced certain data which seemed to indicate a vasomotor effect of sympathetic stimulation on the pulmonary vessels but no effect of parasympathetic stimulation. Weber (1910) reported a change in pulmonary arterial pressure due to stimulation of the central end of the divided vagus nerve. Schafer (1920) reported reflex lowering of pulmonary arterial pressure due to stimulation of the depressor nerve. Hall (1923) observed constriction of the arterioles in the cat's lung produced by adding adrenin to the circulating blood. Certain other investigators including Brodie and Dixon (1904), Erikson (1907), Baehr and Pick (1913), Romm (1924), Lohr (1924),

and Dixon and Hoyle (1928), obtained no conclusive evidence of an effective vasomotor innervation of the pulmonary vessels

By the use of perfusion preparations LeBlanc and van Wijngaarden (1924) Berry and Daly (1931), Berry, Brailsford and Daly (1931), Daly and von Euler (1932), Franklin (1932) and Hebb (1940) demonstrated both effective pulmonary vasoconstriction and vasodilatation In the experiments of Daly and von Euler excitation of the thoracic vago-sympathetic nerves sometimes elicited strong pulmonary vasoconstriction and sometimes weak vasodilatation The pharmacologic evidence obtained seemed to indicate the existence in these nerves of sympathetic vasoconstrictor and parasympathetic vasodilator fibers In Franklin's experiments, adrenin elicited contraction or no response in the large extrapulmonary veins always contraction in the smaller pulmonary veins and very small responses or none in the intrapulmonary veins In the intrapulmonary veins the response was dilatation about as often as vasoconstriction The constrictor effects of adrenin were reversed by ergotoxine indicating the existence of sympathetic vasodilator mechanisms in addition to vasoconstrictor mechanisms Data reported by Hebb also indicate the occurrence of both vasoconstrictor and vasodilator fibers in the sympathetic bronchial nerves

The results of the experiments cited above seem to warrant the conclusion that the sympathetic supply to the pulmonary vessels includes the vasoconstrictor fibers and at least some vasodilator fibers but vasodilator fibers also are included in the parasympathetic supply In general, the effect of the vasoconstrictors is more marked than that of the vasodilators Either vasodilatation or vasoconstriction may take place independently of changes in the caliber of the bronchi, consequently it may be assumed that the pulmonary circulation under physiologic conditions is subject to regulation at least in some degree, through vasomotor nerves In view of the mechanical conditions which obtain it must be apparent that the regulation of the pulmonary circulation depends in a large measure on the regulatory control of the systemic circulation

Bronchial Neuroses —In view of the reactions of the bronchi and bronchial vessels to both direct and reflex vagus and sympathetic stimulation, it is clear that disturbances of the pulmonary innervation might result in asthmatic attacks Not all forms of bronchial asthma however are to be regarded etiologically purely as neuroses In many instances the pathological nervous manifestations associated with asthmatic disease probably represent the result of catarrhal inflammations of the bronchial mucosa On the other hand, inflammation of the bronchial mucosa, under certain conditions may arise as a manifestation of a primary disturbance of the bronchial innervation In any case, asthmatic disease involves profound disturbances of the bronchial innervation

That asthmatic attacks may be brought about by reflex stimulation of various afferent nerves, *e g*, those supplying the nasal mucosa, is well known Likewise strong emotional disturbances not infrequently are accompanied by bronchospasm The so-called sexual asthmas, *i e*, asthmatic attacks which follow disturbances of the sexual apparatus must also be regarded as manifestations of reflex stimulation That the more severe attacks of asthmatic women regularly coincide with their menstrual periods is a fact of common clinical observation To what

along the respiratory tract, sustain a peculiarly intimate functional relationship to the respiratory center. The commonly observed physiologic effect of afferent vagus stimulation is inspiratory inhibition. If both vagi are cooled until they cease to conduct inspiration is both lengthened and deepened probably due to the absence of inhibitory impulses, expiration is not appreciably altered. A like result may be obtained by extirpation of the inferior colliculi. Bilateral vagotomy combined with this operation results in inspiratory spasm. The inferior colliculus apparently includes a center which exerts an inhibitory influence on the respiratory center and functions concurrently with vagus stimulation.

Section of both vagi in the neck alone immediately alters the character of the respiratory movements. The rate is retarded, the amplitude is increased, inspirations become longer and deeper and are followed by an appreciable pause. Section of only one vagus may result in an intermediate effect, i. e., the respiratory rate is retarded somewhat and inspiration is slightly deepened. It may be assumed therefore that some influence which normally maintains the respiratory movements at a more rapid rate has been cut off. This influence consists in the tonic action on the respiratory center of impulses conducted by the afferent vagus fibers which are distributed to the lungs. It constitutes one of the major factors in the maintenance of normal respiratory rhythm. When these vagus fibers are severed the respiratory center drops into a slower, unregulated rhythm. Expansion of the alveoli during inspiration gives rise to vagus impulses which depress the respiratory center and result in inhibition of inspiration (Hering and Breuer, 1868). According to Einthoven (1908), the collapse of the lungs on expiration gives rise only to very weak action currents in the vagus nerve. In experiments designed to reveal the relations of impulses in the pulmonary branch of the vagus to the phases of respiration Partridge (1933) obtained no evidence that either normal or artificial maximal deflation of the lungs stimulates the pulmonary vagal endings but inflation of the lungs initiated afferent impulses. The frequency of these impulses increased during the period of expansion of the lungs. The increase was related to the volume of inspiration but was independent of the rate of expansion of the lungs. Obviously, inspiration requires no vagus stimulation, but is the natural function of the respiratory center. Cessation of the inhibitory influence of vagus stimulation probably is sufficient to release the inspiratory impulses which are held in abeyance during expiration. The increase in lung volume during inspiration initiates impulses which inhibit the inspiratory center, thus limiting the duration and amplitude of inspiration. The decrease in lung volume during expiration tends to limit its duration and amplitude due to removal of the stimulus which initiates the inhibitory impulses (van Voorthuysen and Braak, 1936).

Stimulation of the central end of the divided vagus affects the respiratory center in a variety of ways, depending on the strength of the stimulus and the condition of the center. Such stimulation usually inhibits the respiratory movements partially or completely, resulting either in smaller movements or complete cessation of respiration with the thorax in the condition of passive expiration. On the other hand, the rate of the respiratory movements may be increased until respiration ceases with the thorax in an inspiratory position and the inspiratory muscles in a state of tetanic

contraction These two main effects of stimulation of the central end of the vagus have been interpreted as indicating that the afferent vagus fibers which are distributed to the lungs are of two kinds, each of which has a specific effect (a) inspiratory fibers, whose influence tends to increase the rate of respiration by increasing the rate of inspiratory discharge from the respiratory center, and (b) expiratory (or inspiratory inhibiting) fibers, whose influence tends to retard the rate of respiration by inhibiting the inspiratory discharges from the respiratory center either partially or completely The results of Adrian's (1926) studies involving measurements of the action currents, seem to indicate but one type of afferent vagus fibers to the lungs, which are stimulated by pulmonary inflation but not by deflation Keller and Loser (1929) advanced certain data which seem to indicate that the same afferent fibers may be stimulated in varying manner and intensity by the varying deformations of the lungs According to Hammouda and Wilson (1935), the fibers in the pulmonary branches of the vagi which conduct impulses which excite the respiratory center are of smaller caliber than those which conduct impulses which inhibit this center Their experimental data support the assumption that augmentor impulses are constantly reaching the respiratory center from the lungs, but inhibitory impulses are not initiated at or below the level of normal expiratory expansion They have regarded the retardation of the respiratory rhythm following vagotomy as due to the absence of augmentor impulses

Data obtained in a later experimental study reported by Hammouda, Samaan and Wilson (1943) support the assumptions that both respiratory accelerator and respiratory inhibitory vagus afferents conduct impulses from receptors located within the tissues of the lungs and that all reflex changes in respiration which accompany inflation or deflation of the lungs are elicited by impulses arising in these intrapulmonary receptors They do not support the point of view advanced by Hess (1930) and Gesell, Steffensen and Brookhart (1937) according to which respiratory reflexes following inflation or deflation of the lungs are regarded as at least in part, due to impulses arising in receptors in the thoracic wall or the diaphragm In the experiments of Hammouda *et al*, the inflation and deflation reflexes were not affected by elimination of all afferent impulses from the thoracic walls, the diaphragm and the parietal pleura or by section of the cardiac branches of the vagi and extirpation of the carotid sinus Circulatory changes within the lungs also have no direct effect on these reflexes These findings do not militate against the theory that normal respiration may be carried out through the respiratory center independently of afferent vagus impulses

Since afferent vagus stimulation commonly results in cessation of rhythmic inspiration, the vagi have been regarded as inspiratory inhibitory nerves This interpretation does not take account of the expiratory activity frequently elicited by vagus stimulation and its reciprocal inhibitory action on the inspiratory portion of the respiratory center Artificial inflation of the lungs, which presumably affords adequate and selective stimulation of the pulmonary stretch receptors may result in selective reinforcement of either the inspiratory or expiratory act (Worzniak and Gesell 1939, Gesell and Moyer, 1941) Every stretch receptor therefore probably is synaptically connected with both inspiratory and expiratory

neurons in the respiratory center In experiments reported by Gesell and Hamilton (1941), faradic stimulation of the vagus nerves beginning during the expiratory phase resulted in intensification and prolongation of the period of expiratory activity, thus preventing the normally recurring inspiratory cycles Similar stimulation begun during the inspiratory phase frequently resulted in intensifying the inspiratory act which immediately gave way to a sustained expiratory response They, therefore, regarded the pulmonary vagus, in which proprioceptive fibers predominate, as mainly expiratory Faradic stimulation of the carotid sinus nerve, in which chemoreceptive fibers predominate, in their experiments, resulted in a rhythmic form of breathing faster or slower than normal, in which the depth of both inspiration and expiration was increased Since the inspiratory action was most pronounced they regarded this nerve as predominantly inspiratory Faradic stimulation of the saphenous nerve, in which nociceptive fibers predominate in the experiments of Gesell and Hamilton, resulted in a rapid rhythmic form of breathing in which both inspiration and expiration frequently were equally increased in intensity They, therefore regarded the action of sensory cutaneous nerves on the respiratory center as approximately midway between that of the vagus and that of the carotid sinus nerve

Intermittent faradic stimulation of any one of these nerves, carried out to vary the incidence of stimulation with respect to the phase of the respiratory act, commonly resulted in selective excitation of either inspiratory or expiratory neurons in the respiratory center, depending on the phase of respiratory activity existing at the moment of stimulation The sensitivity of the inspiratory and expiratory neurons, therefore, seems to depend on the prevailing phase of activity Such selective activation of normally discharging inspiratory and expiratory neurons illustrates the principle of precedence of stimulation which, according to Gesell and Hamilton, obtains also for more abnormal conditions of respiration When respiratory rhythm was abolished and replaced by prolonged artificial expiratory contraction by vagus stimulation in their experiments, stimulation of either the saphenous or the carotid sinus nerve resulted in intensification of that contraction without inspiratory complications When sustained expiratory activity, due to intermittently interrupted vagus stimulation, was converted into a slowly developing inspiration by intravenous injection of sodium cyanide, the reflexogenic inspiration was reinforced by every vagal stimulation These reactions illustrate the selective addition of the effects on the respiratory center of the diverse components of very unlike afferent nerves This selective summation of impulses arising in receptors of diverse types indicates their common action in the respiratory center and emphasizes the primary importance of the principle of precedence of stimulation (Gesell and Hamilton 1941)

According to Cromer and Ivy (1933) the central respiratory mechanism is sensitized to vagus inhibition by removal of the stellate ganglia In their experiments, respiratory death was produced in animals with the stellate ganglia removed by continuous strong central stimulation of the vagi, a result which is obtained only rarely in animals with the stellate ganglia intact unless the anesthesia is very deep They also observed that impulses of pulmonary origin which enter the spinal cord *via* the thoracic nerve play a role in the regulation of the central respiratory mechanism

In experiments reported by Cromer, Young and Ivy (1933), afferent impulses initiated by insufflation of ammonia vapor into the trachea reached the respiratory center *via* both the vagi and the upper thoracic nerves. The predominant reflex effect of such stimulation was inhibition of respiration, which was markedly reduced by bilateral section of the vagi or bilateral extirpation of the stellate ganglia. Bilateral section of the vagi and extirpation of the stellate ganglia abolished all the respiratory effects of insufflation of ammonia except a decrease in the air exchange which was regarded as due to bronchoconstriction. In experiments reported by Brookhart *et al* (1936), extirpation of the stellate ganglia, with the vagi intact, had no demonstrable effect on lung-volume-rhythm reflexes. Subsequent bilateral vagotomy abolished these reflexes. The impulses which elicit them obviously are conducted by the vagi.

Normal quiet expiration may be regarded as a purely passive process. The inspiratory muscles are relaxed and the displaced masses return to a resting position due to the force of gravity and the normal elasticity of the tissues involved. The collaboration of the lungs themselves in this process is augmented by their almost ideal elasticity which becomes effective as soon as the intrathoracic pressure begins to rise following inspiration. On the other hand, under conditions of physical exertion or dyspnea, passive expiration no longer suffices and expiration, though still automatic, becomes an active process.

Pressoreceptive Regulation.—The pressoreceptive mechanisms, so important in cardiovascular regulation (see Chapters VII and VIII), also play a significant rôle in the reflex regulation of respiration (Heymans *et al*, 1926–1938, Hering, 1927, Danielopolu and Marcu, 1931, Gollwitzer-Meier and Schulte, 1931). Changes in intravascular pressure acting on the pressoreceptors in the cardio-aortic zone initiate impulses which influence the respiratory center as well as the vasomotor center. An increase in blood pressure in the cardio-aortic area elicits reflex inhibition of the respiratory center, or even apnea, lowering of the cardio-aortic pressure results in the opposite respiratory response.

A decrease in the cephalic blood pressure and blood flow, due to occlusion of the common carotid arteries, produces hyperpnea while an increase inhibits the activity of the respiratory center. These results have been interpreted by some as indicating that the activity of the respiratory center is regulated by changes in its blood supply but, as Pagano (1900) pointed out, the activity of the respiratory center is altered much more profoundly following occlusion of the carotids than following occlusion of the vertebral arteries although the latter are more important for the blood supply of the brain stem. Data advanced particularly by Danielopolu (1926) Hering (1927) and Koch (1931) support Pagano's conclusion that the effects on the respiratory center of changes in carotid blood pressure are due to nerve impulses conducted by the carotid sinus nerve. Blood pressure changes in the aortic arch likewise influence the activity of the respiratory center. A rise in intra-aortic pressure elicits reflex respiratory inhibition, even apnea, a fall results in reflex hyperpnea. Venous pressure also may influence respiration reflexly. In experiments reported by Harrison *et al* (1932) an increase in pressure in the vena cava and the right atrium elicited reflex augmentation of respiratory activity, even hyperpnea.

Experimental data reported by Partridge (1939) support the assumption

probably are continually active under any circumstances compatible with life Most of them probably become active only when the stimulus level is increased With increasing concentration of the stimulating agent, those already active become increasingly effective and more and more other ones begin to discharge impulses As determined by Schmidt and Comroe (1940), the quantum of increased reflex activity required to elicit a measurable increase in effector response corresponds to the measured thresholds Once large numbers of receptors are involved, a further increase in the stimulus results in a greater response than was elicited previously by a similar increase, due to the greater number of receptors involved in each increment The number of chemoreceptors which are continually active under conditions of rest probably is relatively small Under these conditions their physiologic significance also is slight Whether some of the chemoreceptors respond to one stimulus and some to another or whether all respond to the same stimuli as yet is unknown

Modified Respiratory Rhythms—Under normal physiologic conditions vagal end organs are stimulated by distention of the lungs, thus bringing about reflex deflation, which is followed by the inspiratory act (Hering Bruer reflex) Either inflation or deflation of the lungs results in changing the vagal impulses so that the opposite phase is encouraged Afferent vagal impulses thus play a role in regulating the length of each phase and consequently, exert an influence in the control of the respiratory rhythm

When inspiration is forced for a few minutes, the desire to breathe again may not be experienced for three-quarters of a minute or longer A condition of apnea exists which is followed by frequent shallow breathing but the normal rhythm is gradually restored Vagal impulses arising in the lungs are not the major factors in this reaction, since overventilation produces apnea in animals in which the pulmonary branches of both vagi are interrupted The apneic pause probably is due mainly to excessive elimination of CO_2 from the blood, which affects both the respiratory center and the peripheral chemoreceptors

Overventilation of the lungs by an increase in the volume of air breathed (hyperpnea) may be brought about by impulses reaching the respiratory center from the cerebral cortex the hypothalamus or the periphery Conditions which increase the demand of the tissues for oxygen, *e g*, muscular exercise are particularly effective Since the respiratory center is relatively insensitive to lack of oxygen in the blood, hyperpnea induced by muscular exercise probably is essentially reflexogenic Associated changes in the CO content of the blood also exert a direct effect on the respiratory center

Periodic breathing, *e g*, the Cheyne-Stokes type, is characterized by a period in which the individual respirations are shallow and slow at the beginning but gradually increase in depth and rate to a maximum and then subside until they finally cease for a short time This involves an interval of activation of the respiratory center followed by an interval of depression The oxygen lack is intensified by the shallow breathing during the depressed state of the respiratory center This acts as a stimulus to the chemoreceptors and probably increases the sensitivity of the respiratory center to CO The respiratory movements increase in vigor but subside as the CO_2 tension is reduced Reduction of the CO_2 tension of the blood below the level at which the center is stimulated results in the temporary

apnea, which in turn increases the oxygen lack and prevents the elimination of CO. Thus the center is stimulated and the respiratory movements are reestablished but cease again when sufficient O has been absorbed and sufficient CO_2 eliminated to prevent further excitation of the center. Under normal physiologic conditions, any sudden decrease in the CO tension of the blood supplying the respiratory center is prevented by the store of CO which the body holds in the lungs and the tissue fluids. Any sharp increase in CO tension is prevented due to the buffering of the excess CO by the tissue fluids.

Respiratory Reflexes from the Upper Air Passages.—Stimulation of the sensory fibers supplying the nasal mucosa (trigeminal) by injurious or irritating gases elicits reflex inhibition of respiration. A similar effect may be obtained by stimulation of the sensory fibers supplying the pharynx (glossopharyngeal). Indeed, every act of swallowing elicits temporary inhibition of respiration through the glossopharyngeal nerve. Mild irritants and odorous substances also elicit reflex modification of the respiratory movements. According to Allen (1929), inhalation of such substances commonly causes either a lowered respiratory phase and an increase in the rate of the excursions or a deepened inspiratory phase and a decrease in the rate of the excursions. The reflex responses to disagreeable odors and mild irritants commonly are stronger than those to agreeable ones. Odorous substances which are not irritating elicit no reflex respiratory responses in anosmatic subjects. The respiratory response to odors is mediated through the olfactory reflex system. The reflex inhibition of respiration elicited by stimulation of the sensory fibers distributed along the upper air passages may be regarded as a reaction which automatically protects the lungs from injurious gases. The protective character of this reaction is evidenced by the fact that reflex closure of the larynx occurs simultaneously with the cessation of respiration and, if the stimulation is strong enough, the bronchial musculature also contracts, so that the passage to the alveoli is made still more difficult. Although this reflex cessation of respiration is only temporary, it is automatic and affords at least a short interval before the inhibition is broken through by the increasing irritability of the respiratory center, during which the individual may escape from a dangerous locality. In certain animals, *e. g.*, certain of the water birds, reflex inhibition of respiration may be maintained for relatively long intervals. This undoubtedly is a special adaptation of the reflex to meet the requirements of diving. The reflex coughing caused by irritating gases or foreign bodies which enter the larynx may be regarded as an automatic but purposeful attempt to expel the stimulating object. In the act of coughing, the rima glottis which shortly before was closed is forced open by a sudden explosive expiration. This involves not only reflex inhibition of the inspiratory movements, but also reflex excitation of expiratory movements of a peculiar type. The coughing reflex may be elicited by stimulation of the vagus fibers distributed to any part of the respiratory tract (Staehelin, 1914) but is not elicited from all the areas of vagus distribution in the respiratory tract with equal facility. Stimulation of the deeper parts of the larynx is most effective. The facility with which this reflex is elicited gradually decreases, approaching the smaller subdivisions of the bronchial tree. It also is rarely elicited by irritation of the pharynx and the base of the

tongue On the other hand, the coughing reflex may be elicited by stimulation of the afferent vagus fibers supplying various visceral organs, *e g* the liver and spleen It has also been observed clinically that under certain conditions irritation of the parietal pleura elicits the coughing reflex

Sneezing also may be regarded as a protective respiratory reflex In this instance the posterior nares just previously closed by contraction of the superior constrictor muscles of the pharynx is forced open by explosive expiration This reflex is elicited most commonly by stimulation of the afferent fibers (trigeminal) supplying the nasal epithelium It serves to remove mucus or other extraneous matter from the nasal mucosa

Other Special Respiratory Reflexes —Yawning is in part a respiratory reaction which may be regarded as a type of indirect vascular reflex which serves the purpose of improving the circulation (Regelsberger 1924) Simultaneous stretching reflexes not uncommonly aid in this process The stretching and yawning reflexes, according to Dumpert are intimately associated in their phylogenetic origin Man, therefore, is able only by practice to separate these two reflexes and to suppress the stretching reflex entirely It is interesting to note in this connection that not uncommonly in cases of hemiplegia yawning is accompanied by forced stretching movements in the paralyzed limbs This suggests the primitive origin of the reflexes and their incorporation in the reflex pattern of the older parts of the brain The frequent occurrence of yawning in cases of brain tumor and encephalitis also suggests the primitive origin of this reflex

Sobbing, laughing and weeping involve forced automatic movements, particularly of the larynx and diaphragm, which affect respiration and are coordinated with the movements of expression These reflexes are elicited by emotional states Although in most instances they may be inhibited voluntarily in greater or less degree, they are carried out through centers which are essentially automatic

Hiccough is a respiratory reflex which is purely automatic and, in most instances not subject to voluntary inhibition The familiar phonation accompanying this reflex is inspiratory It is caused by suction of air past the just closing vocal folds by spastic contraction of the diaphragm The diaphragmatic movement consists essentially of a short sudden beat The afferent impulses commonly are conducted by afferent fibers in the phrenic nerve but the stimuli which elicit this reflex are obscure Hiccough may arise without any apparent cause and persist for a short or a long interval Hiccough of short duration may be regarded as a harmless disturbance of respiration but when it persists for a relatively long time, as it not infrequently does in certain pathologic conditions it becomes a matter of grave clinical importance because of its effect on the general physical condition of the patient

Hiccough not infrequently is caused by irritation of the phrenic nerve It occurs commonly in cases of aortic aneurism carcinoma in the region of the root of the lung and in all affections of the diaphragm It occurs frequently also in cases of peritonitis and carcinoma of the stomach, liver, kidney or adrenal gland It has also been reported in operations for hernia It usually is a reflex phenomenon Regelsberger (1924) has pointed out that the stimuli which elicit this reflex may arise throughout the entire area of distribution of the phrenic nerve and the sympathetic fibers con

nected with this nerve The phrenic nerve undoubtedly plays a major role in the afferent conduction of these impulses

In certain cases, hiccough arises not as a reflex phenomenon but as a result of stimuli arising in the blood, *e g*, in cases of uremia acetonemia and venous stasis in the region of the medulla oblongata In such cases certain cells in the brain stem probably react to toxic substances in the blood Hiccough may also arise as a result of psychic disturbances and in cases of organic diseases of the central nervous system The existence of a special center in the brain which mediates this peculiar respiratory phenomenon seems improbable It probably is carried out through the general respiratory center

CHAPTER X

INNERVATION OF THE DIGESTIVE TUBE

Extrinsic Nerves.—Pharynx.—The pharynx derives its innervation from the glossopharyngeal, vagus and sympathetic nerves. The glossopharyngeal supplies mainly the upper portion, the pharyngeal branches of the vagus, the middle and lower portions. Where the branches of the glossopharyngeal and vagus meet they enter into a plexus formation which, together with some of the sympathetic rami supplying the pharynx, constitutes the pharyngeal plexus. The sympathetic supply to the pharynx is derived mainly from the superior cervical ganglion. Some of the sympathetic fibers enter the pharyngeal plexus through separate sympathetic rami, others become incorporated in the pharyngeal branches of the vagus, before reaching the pharynx and join the plexus with these nerves. Still others pass directly to the pharyngeal musculature without taking part in the plexus formation. The majority of the sympathetic fibers seem to be distributed to the lower portion of the pharynx.

Esophagus.—The esophagus is innervated through the vagus and sympathetic nerves. The vagus supply to the cervical portion is derived from the recurrent nerve through parallel branches which enter the esophageal wall. In general, these branches neither cross the medial plane nor enter into a plexus formation. In the thorax, both vagi lie in close proximity to the esophagus and supply branches to it. Two or three branches of the right vagus commonly join the left at this level. The distribution of each vagus nerve to the thoracic portion of the esophagus is not confined to its own side but each nerve also sends branches to the opposite side. The left vagus supplies mainly the anterior surface and the right vagus mainly the posterior surface of this portion of the esophagus.

The sympathetic nerves supplying the esophagus arise mainly from the inferior cervical or stellate ganglion. Some fibers arising in the cervical sympathetic ganglia also reach the esophagus through communications of the sympathetic cardiac nerves with the recurrent branch of the vagus. One or more rami arising from the stellate ganglion join the recurrent nerve, others either join the vagus trunk or pass directly to the esophagus. Some of the thoracic rami pass directly to the esophagus, others join the aortic plexus and supply fibers to the esophagus through this plexus. The lower portion of the esophagus also receives sympathetic fibers via the plexuses on the left gastric and inferior phrenic arteries (Mitchell, 1938) and via the greater splanchnic and occasionally the lesser splanchnic nerve. In the posterior mediastinum, the sympathetic nerves and the vagi with their intercommunicating branches constitute a plexus surrounding the esophagus (esophageal plexus). Branches arising from this plexus penetrate the esophageal wall.

Stomach.—The stomach, like the esophagus, is innervated through the vagus and sympathetic nerves. From the esophageal plexus both vagi continue onto the stomach where each commonly breaks up into a left, a middle and a right division. As the left vagus passes downward over the anterior aspect of the stomach, its left division supplies branches to the

fundus and approximately the upper two thirds of the corpus, its middle division supplies the prepyloric region, its right division passes to the liver. As the right vagus passes downward over the posterior aspect of the stomach, its left division supplies the cardia, the lesser curvature and a greater or lesser portion of the corpus, its middle division supplies the prepyloric region, its right division joins the right celiac ganglion. Not infrequently

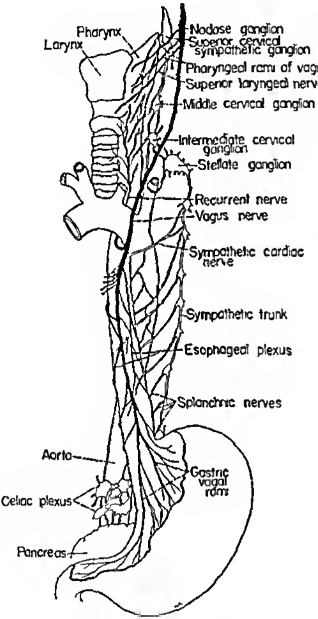


FIG. 52.—Diagrammatic illustration of the extrinsic nerves of the pharynx, esophagus and stomach.

branches of both vagi anastomose and form a plexus at the right side of the cardia from which fibers are supplied to the cardiac region. In the prepyloric region, branches of the middle division of both vagi enter the hepato-gastric ligament.

The sympathetic innervation of the stomach is derived mainly from the celiac plexus. Most of the fibers accompany the various gastric arteries. The proximal portion also receives sympathetic fibers from the left and

occasionally the right phrenic plexus, the left gastric plexus and the hepatic plexus (Mitchell 1938, 1940) A few rami arising from the upper lumbar segments of the sympathetic trunk also join the stomach In the hepatogastric ligament, sympathetic fibers derived from the celiac plexus mingle with vagus fibers as both approach the stomach These fibers do not form an intricate plexus but, in general bundles of vagus and sympathetic fibers lie parallel to one another The fibers derived from the hepatic plexus also traverse the hepatogastric ligament Mitchell (1940) proposed that these fibers be designated the hepatogastric nerves

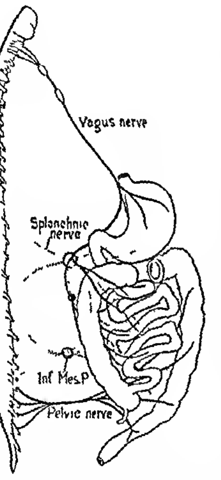


Fig 53 —Diagram illustrating the distribution of sympathetic and parasympathetic nerves to the stomach and intestine

In the dog according to Bilchum and Weaver (1943), visceral afferent components of all the spinal nerves from the eighth thoracic to the thirteenth reach the stomach via the splanchnic nerves In some instances afferents from the stomach enter the spinal cord as far cephalad as the fourth thoracic nerve and in some as far caudad as the second or third lumbar

Small Intestine —The small intestine like the stomach is innervated through both vagus and sympathetic nerves The vagus supply is derived mainly through the division of the right vagus which joins the celiac plexus The sympathetic fibers are derived mainly from the celiac and superior mesenteric plexuses Both sets of fibers enter the small intestine through the mesenteric nerves which, in general, accompany the mesenteric arteries Vagus and sympathetic fibers can be distinguished from one another by differences in caliber and their distribution in the intestinal wall After leaving the celiac plexus the vagus fibers form bundles which either take independent courses in the mesentery or accompany the larger blood vessels and usually enter the intestinal wall with the latter They penetrate the subserosa and longitudinal muscle layer and enter the myenteric plexus Some extend farther toward the mucosa and enter the submucous plexus The sympathetic nerves in general, are more intimately associated with the mesenteric vessels They anastomose freely in the subserosa Most of the fibers enter the intestinal wall in close association with the larger vessels others form a plexus in the subserous layer The latter probably are mainly general visceral afferent fibers

Large Intestine —The cecum, vermiform appendix and ascending and transverse portions of the colon are innervated through nerves which arise

directly from the superior mesenteric plexus These nerves include both vagus and sympathetic fibers The descending colon and upper part of the rectum are supplied by nerves which arise from the inferior mesenteric plexus The portion of the large intestine supplied by vagus fibers varies somewhat in different animals The exact distribution of efferent vagus fibers to the large intestine in man is unknown The parasympathetic supply to the descending colon and rectum is derived mainly through the sacral outflow, the preganglionic fibers involved being components of the

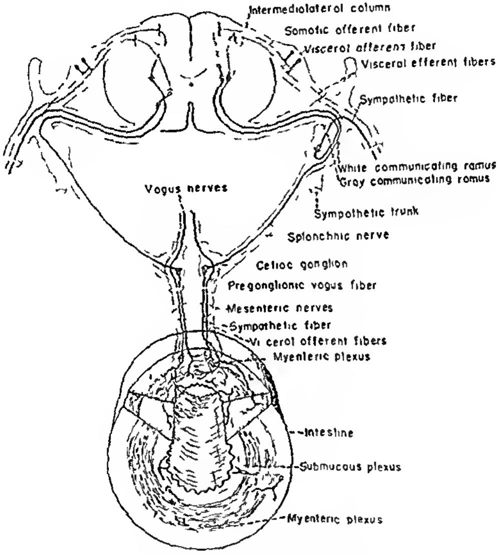


FIG 54 —Diagram illustrating the sympathetic parasympathetic and afferent conduction pathways to the small intestine

visceral rami of the second and third or third and fourth sacral nerves The major portion of the parasympathetic supply to the distal colon in man is independent of the hypogastric plexus The fibers constitute a small but definite trunk derived from the pelvic nerves on either side which, after traversing the pelvic plexuses, ascends on the left side of the hypogastric plexus (Telford and Stopford 1934, Trumble, 1934) The lower part of the rectum is supplied by sympathetic fibers derived from the upper and lower divisions of the hypogastric plexus These fibers accompany the superior and middle hemorrhoidal arteries The inferior hemorrhoidal

plexus in the small intestine (Greving, 1931) but includes fewer ganglia and ganglion cells

The submucous plexus in the esophagus consists of a meshwork of very slender fiber bundles. According to various investigators, particularly Greving (1920) and Thomas (1931), no ganglia occur in the esophageal submucosa. The major portion of the submucous plexus in the esophagus lies close to the muscularis. It is intimately connected with the myenteric plexus by numerous fiber bundles and fibers extend from it into the mucosa where many of them terminate either in the epithelium or in the sub-

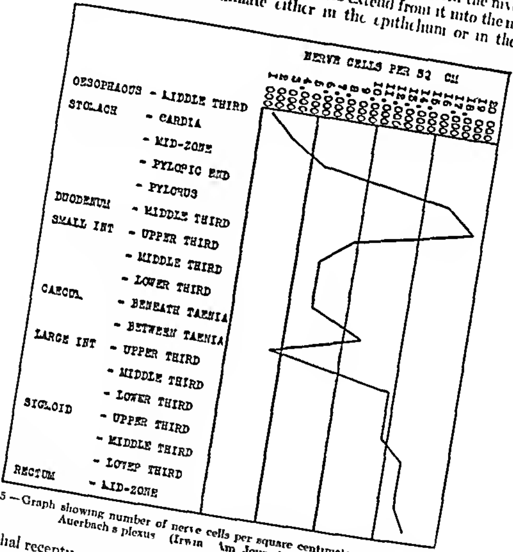


FIG 55 — Graph showing number of nerve cells per square centimeter at various levels of Auerbach's plexus (Irwin, Am Jour Anat, 1930)

epithelial receptive end organs. The latter fibers are relatively large. They are mainly visceral afferent components of the vagus and thoracic nerves. Afferent fibers also terminate in the esophageal musculature.

In the stomach both the myenteric and the submucous plexuses exhibit the same general plan of structure as in the small intestine. According to Irwin (1931) both the fiber bundles and the ganglia are small and few in the cardiac region but increase materially both in size and number toward the mid gastric zone and more gradually from this zone toward the pylorus. The submucous plexus is more abundantly developed in the stomach than in the esophagus but includes relatively few ganglia

In the large intestine, the enteric plexuses exhibit the same general plan of structure as in the small intestine (Schmidt, 1931). In the guinea-pig, the ganglia of the myenteric plexus are aggregated beneath the longitudinal muscle bands (taenia coli) to some extent, leaving the intervening longitudinal zones with relatively few ganglia (Irwin, 1931). The rectal portion of the myenteric plexus is particularly rich both in fibers and ganglia. It terminates abruptly at the level of the internal sphincter, to which it supplies efferent fibers. According to Ottaviani (1940), the rectal columns are abundantly innervated through nerves which include many fibers of somatic type. The innervation of the internal and external anal sphincters, according to his findings, involves a common plexiform structure which includes many fibers of somatic type.

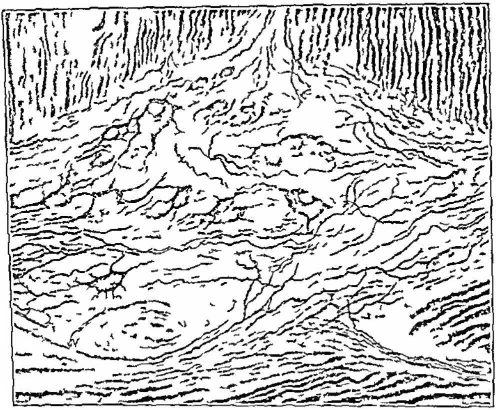


FIG. 56.—A ganglion in the myenteric plexus drawn from a tangential section of the intestine of the dog (pyridine silver).

The enteric ganglia and their constituent neurons are not uniformly abundant throughout the digestive tube but vary within a relatively wide range both in the myenteric and the submucous plexus. The numbers of ganglion cells per sq. cm. in the myenteric plexus at successive levels in the digestive tube of the guinea-pig, as determined by Irwin (1931) show a rapid rise from the middle third of the esophagus to the pylorus, then an abrupt fall in the upper third of the small intestine, another marked rise in the upper third of the colon and a more gradual rise from this level to the anal sphincter (Fig. 55). These findings have been corroborated by those of Matsuo (1934).

Actual counts of ganglion cells in the submucous plexus are not available. As stated above, this plexus includes no ganglion cells in the esophagus and relatively few in the stomach. Ganglion cells are present in considerable

abundance throughout the small intestine and, according to Müller (1924), in greater abundance in the large intestine, particularly the rectum

The Enteric Ganglion Cells —Most of the enteric ganglion cells are multipolar, but bipolar and unipolar neurons also have been described in the enteric plexuses (Hill, 1927) On the basis of very careful histologic studies, based mainly on Bielchowsky preparations of the intestine of man and other mammals, Müller (1911) concluded that the enteric ganglion cells differ sufficiently in their morphologic characters from the neurons in other parts of the autonomic system to set them off as a distinct type This difference involves the size and general structure of the cell body less than the character, arrangement and distribution of the dendrites, and the relation of the ganglion cells to the adjacent tissues In a more recent study involving measurements of the dimensions and comparison of the form and general structure of the cell bodies of neurons in the enteric ganglia and those in the ganglia of the sympathetic trunk Johnson (1925) found no morphologic differences by which he could clearly differentiate the former from the latter His studies did not take into consideration the exact arrangement and distribution of the dendrites

According to Müller, the myenteric plexus includes ganglion cells of two types Those of the one type lie quite free in the intermuscular spaces, those of the other sustain a peculiarly intimate relationship to the muscle In sections of a flattened piece of intestine taken in the plane of the myenteric plexus, the cell bodies of the former type usually appear rounded in outline and their dendrites, which are relatively broad at the base taper distally and radiate in all directions, may be traced for some distance from the cell body In some instances dendrites of neurons of this type terminate in foot-like enlargements in contact with the adjacent musculature Not infrequently a single process probably the axon may be traced into the muscle The neurons of the latter type usually lie in close proximity to the musculature The cell body commonly is elongated or pyriform and lies with its long axis parallel to the adjacent muscle It usually gives rise to relatively large cone-shaped processes at the side toward the muscle These processes, some of which give rise to terminal branches, terminate in small foot like expansions in direct contact with muscle cells Every ganglion cell gives rise to one longer process which Müller regarded as the axon Not infrequently one of these ganglion cells may be observed in a slight depression in the muscle at the periphery of the ganglion Cells of this type, as Müller suggested, are of peculiar interest due to their intimate relationships, through their short dendrites, to the musculature They are less numerous than those of the other type Müller emphasized the relatively large number of dendrites arising from some of the neurons in the myenteric ganglia, and stated that a process can frequently be traced from one of these neurons into a fibrous ramus which runs from the ganglion in question to a neighboring one

According to Hill (1927), the neurons in the myenteric ganglia in general conform to Dogiel's Types I and II Those of Type I are characterized by short dendrites and those of Type II by longer dendrites According to her observations, the neurons of Type I are easily recognizable in silver preparations due to their intense staining reaction and their superficial position in the ganglia Their short dendrites not uncommonly form brush-like arborizations on the neurons located deeper and more centrally

in the ganglia More rarely the longer dendrites of the neurons of Type I ramify around the cell bodies of the more centrally located neurons or mingle with the fibers in the intercellular plexus The axons of these neurons, according to Hill, can in some instances be traced for a relatively long distance through neighboring ganglia and fiber tracts, but they generally disappear among the fibers of the intercellular plexus She was unable to trace axons of neurons of Type I either into the musculature or outside the myenteric plexus, consequently, she did not regard these cells as motor in function, but suggested that they may be associative

The neurons of Type II, according to Hill, are larger and more variable than those of Type I Although most of them are multipolar, she regarded the bipolar and unipolar neurons observed in her preparations as belonging to this type The dendrites of these neurons are relatively long and branch freely They commonly extend into a fiber bundle related to the ganglion of origin, and can frequently be traced for a relatively long distance She could distinguish between dendrites and axons of neurons of this type only by their terminations The dendrites commonly terminate in neighboring ganglia The axon eventually passes into the musculature, where it terminates in relation to muscle cells On the basis of these findings, she regarded the neurons of this type as motor in function

Van Esveld (1928) described the neurons in the myenteric ganglia in the cat as conforming almost perfectly to the two types of ganglion cells described by Dogiel He also observed ganglion cells of the same types imbedded in the circular muscle in the intestine either singly or in small groups These occurred most commonly near the mesenteric attachment Stöhr Jr (1930) likewise recognized neurons in the myenteric plexus which conform morphologically to Types I and II of Dogiel but found no reason to regard them as functionally distinct Ito (1936) described ganglion cells of three types, in the human appendix, on the basis of their intimate cytological structure and staining reactions but attached no functional significance to the differences observed He found no significant cytological differences between the ganglion cells in the myenteric plexus and those in the submucous

The length of the axons of the enteric neurons and their longitudinal distribution cannot be determined by direct histological observations In an extensive physiologic investigation using the isolated intestine of the fowl Nolf (1929) found that nicotinization of a segment 8 cm or over in length abolishes longitudinal conduction in the myenteric plexus On the basis of this and other experimental observations, he concluded that the myenteric neurons in the intestine of the fowl are approximately 8 cm in length and that the myenteric plexus includes longitudinal conduction pathways made up of intrinsic neurons which sustain a synaptic relationship to one another He also advanced certain evidence which he interpreted as indicating that the axons of some of the enteric neurons divide dichotomously, sending one division oralward and the other aboralward, the former being approximately 4 5 cm, the latter approximately 8 cm in length These findings have not been confirmed by later investigations

According to the findings of most investigators, the enteric ganglion cells are not enclosed in pericellular capsules In the stomach and intestine according to Greving (1920), numerous cells with small rounded nuclei and no apparent processes lie scattered between the ganglion cells

throughout the ganglia but do not form pericellular capsules Cells of the same kind also occur in the fiber bundles connecting the myenteric ganglia

In the submucous plexus in the intestine, the neurons are more compactly aggregated in the ganglia than in the myenteric plexus They are also less angular in outline, except in instances in which they seem to be pressed together in the ganglionic mass The dendrites of most of these neurons are relatively long and frequently may be traced beyond the borders of the ganglion into the fibrous rami In most instances it is quite impossible to distinguish between the axon and dendrites in this plexus According to Hill (1927), the submucous plexus includes only neurons of Dogiel s Type II Stohr, Jr (1930), on the contrary, recognized neurons of both Types I and II of Dogiel in this plexus The fact that many of the neurons in the submucous plexus send their dendrites far beyond the confines of the ganglion in which the cell body is located as will be pointed out below has an important bearing on the interpretation of the functional relationships of these neurons

Pericellular capsules have not been described in ganglia of the submucous plexus but small cells with rounded nuclei like those described above as lying between the neurons in the ganglia of the myenteric plexus, also are present in the ganglia in this plexus

The Intercellular Plexus —In the ganglia of both the myenteric and the submucous plexus there exists an intraganglionic fiber complex which is made up in part of the processes of the local neurons and in part of fibers of extrinsic origin This fiber complex is more abundant in the myenteric than in the submucous ganglia In the ganglia of either plexus the fibers of extrinsic origin are mainly small unmyelinated fibers which stain darkly in pyridine-silver preparations Those of local origin include both large and small fibers The large fibers represent mainly the short dendrites and the proximal portions of the longer ones The distal portions of the longer dendrites, like the fibers of extrinsic origin, are slender and stain darkly in pyridine silver preparations The large fibers usually run through the ganglion in various directions without showing much evidence of plexus formation The smaller fibers commonly give rise to very fine intercellular plexuses In experiments reported by Johnson (1925), section of all the extrinsic nerves to the intestine or of both vagi below the diaphragm resulted in complete disappearance of the intercellular plexuses in the myenteric ganglia The fibers which remained are clearly the processes of local ganglion cells These fibers, according to Johnson divide repeatedly and terminate in the adjacent smooth muscle Section of the splanchnic nerves alone resulted in no apparent change in the myenteric plexus He, therefore concluded that the splanchnic fibers do not enter into the pericellular plexus in the myenteric ganglia In the animals in which only the vagi were cut, there still remained, in addition to the processes of the local ganglion cells, many small unmyelinated fibers which Johnson regarded as postganglionic sympathetic fibers

The results of these experiments seem to indicate that the pericellular plexuses in the myenteric ganglia which are brought out so well in pyridine-silver preparations are made up of the terminal portions of preganglionic vagus fibers They also indicate that the postganglionic sympathetic fibers which enter the intestinal wall pass through the myenteric plexus but take no part in the formation of the intercellular plexuses If,

as seems highly probable, the synapses of preganglionic with enteric neurons are effected through the intercellular plexuses, these findings conform fully to the current teaching that the efferent vagus fibers to the intestine are preganglionic and enter into synaptic relationship with neurons in the enteric ganglia, while the sympathetic fibers which enter the intestinal wall through the extrinsic nerves terminate in direct relationship to the musculature

According to the above interpretation, vagus and sympathetic fibers sustain the same relationships to the enteric plexuses as to certain other peripheral plexuses, e g , the pulmonary and cardiac plexuses It does not follow that all the neurons in the enteric plexuses are components of vagus efferent chains The great abundance of these neurons has been emphasized by various investigators, and it has seemed to some quite impossible that the preganglionic vagus fibers could effect synaptic connections with all of them Langley (1922) attempted to obviate this anatomical difficulty by postulating intermediate mother cells of vagus origin According to his concept, every vagus fiber presumably effects synaptic connections with a number of mother cells, each of which in turn effects synaptic connections with a number of other enteric ganglion cells Anatomic evidence for the existence of such intermediate neurons in the vagus efferent chains is wanting

Hill (1927) did not agree with Johnson regarding the composition of the intercellular plexuses in the myenteric ganglia She maintained that they are made up in part of the terminal portions of preganglionic vagus fibers and in part of the processes of the enteric neurons This is in full accord with the evidence presented by her in support of the contention that many of the dendrites of the enteric neurons terminate in relation to the cell bodies of neurons in neighboring ganglia or adjacent neurons in the same ganglion, and the conclusion that the axons of some enteric ganglion cells terminate within the myenteric plexus (Kuntz, 1922) The theory that the terminations of preganglionic vagus fibers on enteric neurons constitute the only neuron junctions in the enteric ganglia, therefore is no longer tenable

Anatomic Evidence for the Occurrence of Enteric Reflex Arcs —The existence of local reflex mechanisms in the enteric nervous system is clearly indicated by abundant physiologic data but the anatomic evidence in support of the assumption that some enteric ganglion cells effect synaptic contacts with others in the same or adjacent ganglia is as yet meager

This assumption is supported by certain anatomic data reported by Kuntz (1922) In methylene-blue preparations of the intestine of the cat, an intensely stained process of one ganglion cell could in some instances be traced without interruption to its termination in a pericellular network on the lightly stained cell body of another ganglion cell in the same ganglion or an adjacent one Although these pericellular networks resemble very closely those which have been described in other autonomic ganglia and interpreted as synapses, they might still be regarded as pericellular terminations of dendrites In certain instances fibers which enter the myenteric ganglia from the submucous plexus could be traced to their terminations in similar pericellular networks on the bodies of lightly stained ganglion cells The possibility that these fibers represent dendrites is not precluded, but it appears more probable that they are the axons of ganglion cells in

the submucous plexus If they are axons, the terminations in question must be regarded as synapses Since the fibers extend from the submucous into the myenteric plexus, they cannot reasonably be interpreted as preganglionic fibers of vagus or spinal origin but must be regarded as fibers of enteric origin In both the myenteric and the submucous plexus, fibers could be traced from one ganglion without interruption to pericel-

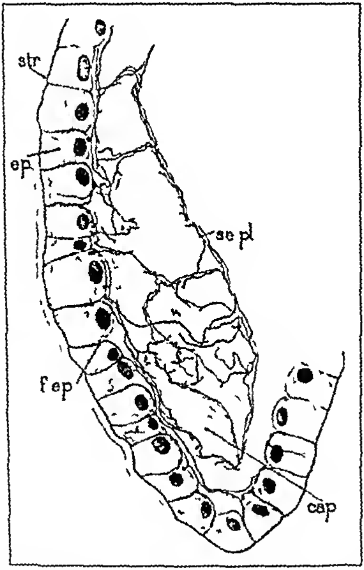


FIG 57.—Subepithelial plexus and nerve terminations between the epithelial cells of a villus in the small intestine of a new born rabbit (silver method of de Castro) (Catherine J Hill) *cap* Capillary *ep* epithelial cell *f ep* terminal branch of a nerve fiber between epithelial cells *se pl* subepithelial plexus

lular terminations of the same type in neighboring ganglia Some of these, particularly in the myenteric plexus might possibly be interpreted as synapses of preganglionic vagus fibers with enteric ganglion cells The intercellular plexuses which, in Johnson's (1925) experiments, underwent degeneration following vagus section and therefore, were regarded by him as effecting the synapses of the preganglionic vagus fibers with enteric neurons are grosser structures and sustain a less intimate relationship to

the cell bodies of the enteric ganglion cells than the pericellular terminations in question. It seems highly probable, therefore, that the latter represent synapses involving two enteric neurons.

According to the current teaching, two enteric neurons which sustain a synaptic relationship to one another cannot be regarded as terminal links of a vagus efferent chain. They must either be interpreted as components of a local reflex arc, even though the dendrites of the one cannot actually be traced to terminations of a recognized sensory type, or the existence of association neurons in the enteric plexuses, as suggested by Hill (1927), must be conceded. Of these two possibilities the former appears the more probable on anatomic grounds. It is also supported by abundant physiologic data which will be considered below.

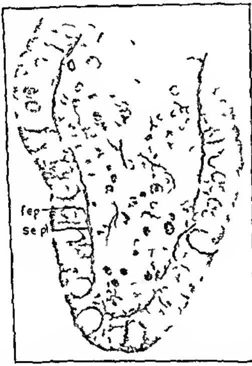


FIG. 58.—Subepithelial plexus and nerve terminations between the epithelial cells of a villus in the small intestine of the dog (pyridine silver). (Waddell.) *f ep*, Terminal branch of a nerve fiber between epithelial cells; *Se pl*, subepithelial plexus.

The results of the work of Johnson (1925), cited above, failed entirely to corroborate these findings. In his preparations of the intestine in which the intercellular plexuses were absent following degeneration of the extrinsic nerves, he found no evidence of synapses in the myenteric ganglia. It may be stated in this connection that the pyridine-silver technic is not adapted to bring out such delicate pericellular structures as those observed in our methylene-blue preparations. Even in these preparations, pericellular terminations could be observed only on ganglion cells which were stained but lightly. Intracapsular pericellular terminations have been described in methylene-blue preparations of other sympathetic ganglia. As far as we are aware such terminations have not been observed in pyridine-silver preparations in any part of the autonomic nervous system. Further investigation of the relationships of enteric ganglion cells to one another, especially by the use of the methylene-blue technic, would be highly desirable.

Nerve fibers of enteric origin, some of which presumably represent dendrites, have been traced to the gastro-intestinal epithelium, particularly in lower vertebrates (Dogiel 1896 Sakusseff, 1897) In methylene-blue preparations of the intestine of the cat Kuntz (1922) traced fibers from the submucous plexus through the muscularis mucosæ into the intestinal villi where some of them were distributed to the muscle fibers which extend into the villi and others terminated in relation to epithelial cells

The Enteric Nerve Net Theory —There has long been a tendency on the part of certain investigators to regard the enteric nervous system as composed, at least in part, of nerve nets characterized by actual protoplasmic continuity between the constituent cellular elements Bethe (1903) and R Muller (1908) described the enteric plexuses in the frog as consisting of true nerve nets Erich Muller (1920) described the enteric plexuses in the Selachians exclusively syncytial In a later paper (1921), he described the enteric plexuses in birds and mammals as consisting in part of syncytial nerve nets and in part of neurons which do not anastomose with one another

Anastomosing nerve cells have been described by Cole (1925) in the myenteric plexus in the frog In methylene-blue preparations, these cells appeared to be connected by broad protoplasmic bands They occurred in groups of two, three or four cells and were found both in the ileum and the rectum The nervous nature of these cells seems to be established by the presence of chromidial substance In most instances an axon could be demonstrated for each cell of a given group Cole regarded these anastomosing ganglion cells as belonging to the same category as binuclear ganglion cells which are not uncommon in the autonomic ganglia in certain animals (Apolant 1896, Carpenter and Conel, 1914) He also pointed out that there is a marked difference between these anastomosing ganglion cells and those found in the typical invertebrate nerve net In the latter axons and dendrites cannot be differentiated, the cell processes are all alike In the anastomosing ganglion cell groups described by Cole, only the dendrites were involved in the intercellular connections

In pyridine-silver preparations of the small intestine of the dog Waddell (1928) occasionally observed two ganglion cells in the myenteric plexus joined together by a single fiber In some instances, the two cells joined together in this manner lay in proximity to each other in others they were removed from each other by a distance equal to several times the diameter of a ganglion cell body His preparations also exhibit ganglion cells joined together in pairs by relatively broad protoplasmic bands The latter cells like the anastomosing ganglion cells described by Cole in the intestine of the frog probably belong to the same category as binuclear ganglion cells We cannot regard the ganglion cells joined together by a single well differentiated fiber as belonging to the same category We do not regard these findings as supporting the theory that the enteric plexuses in mammals are made up even in part of true nerve nets

Nerve Fiber Terminations —Most of the nerve fiber terminations observed in the gastro-intestinal musculature as described by many investigators conform to the mode which is typical for postganglionic autonomic fibers Those which innervate the gastro-intestinal musculature in general lie parallel to the muscle fibers and give rise to numerous branches which

form an intermuscular plexus. Many of the data on which modern concepts of autonomic end-formations are based have been obtained in studies based on preparations of the gastro-intestinal tract. These data are set forth at length in Chapter II.

Afferent nerve fiber terminations also have been described in the gastro-intestinal musculature. Nemiloff (1902) and Cole (1925) described nerve fiber terminations which appear to be of a sensory type in the musculature of the large intestine of the frog. They involve complex arborizations of the terminal unmyelinated branches of myelinated fibers. In methylene-blue preparations, the terminal filaments usually are lightly stained and bear relatively large varicosities which often stain heavily. Carpenter (1918) observed nerve fiber terminations, probably of a sensory type, in the stomach of the cat and the small intestine of the dog. Those in the stomach were described as terminal skeins and nets composed of fine varicose fibers, those in the small intestine as tufts of exceedingly delicate varicose fibers. These structures probably represent the terminal branches of visceral afferent fibers. As Carpenter pointed out, they are so situated that they could be stimulated directly by contraction or distention of the musculature in which the majority of them are located. Smooth muscle spindles also have been observed in the esophagus (Greving, 1931).

The subepithelial plexus in the gastro-intestinal mucosa undoubtedly includes terminal branches of general visceral afferent fibers. It probably also includes the terminal portions of receptive fibers arising in the enteric ganglia. Receptive end organs in the esophageal mucosa and submucosa have been amply demonstrated. Complicated skein-like sensory structures also have been observed in the rectal mucosa (Ottaviani, 1940).

Physiologic Data.—Esophagus.—The esophagus differs structurally from the other divisions of the digestive tube in that its musculature is made up of both striated and smooth muscle fibers. In the dog, the cat and the ape, it consists mainly of striated muscle but includes some smooth muscle in the distal portion. In man, the transition from striated to smooth muscle takes place in the upper thoracic portion of the esophagus, beginning somewhat higher in the anterior than in the posterior wall.

The chief function of the esophagus is illustrated by the swallowing reaction, which may be initiated as a voluntary act, but becomes reflex during its execution. Voluntary initiation of the act of swallowing requires the presence of liquid or solid matter in the pharynx. In the absence of food or other foreign matter, a little saliva is passed backward by the tongue which serves as a mechanical stimulus for the initiation of the reflex reaction. Voluntary deglutition is impossible when the mouth is entirely free of saliva. The swallowing reaction also may be elicited as a pure reflex by stimulation of certain areas of the mucosa of the mouth and pharynx. These areas vary somewhat in different animals but the afferent impulses involved are conducted by fibers of the trigeminal, glossopharyngeal or vagus nerves. The superior laryngeal branch of the vagus probably is involved most commonly in such afferent conduction. The glossopharyngeal nerve also conducts impulses which inhibit the swallowing reflex. The efferent impulses involved in the swallowing reaction are conducted mainly through the glossopharyngeal and branches of the vagus nerves. Fibers of the hypoglossal nerve and the mandibular division of the trigeminal also play a part. The motor innervation of the esophagus

involves the recurrent and certain thoracic branches of the vagus, the sympathetic supply and the intramural plexuses. The sympathetic nerves probably play no significant part in the swallowing reflex. According to Inouka (1924), the effective innervation of the esophagus in the dog is purely vagal. Knight (1934) reported reduction in tonus of the musculature in the distal portion of the esophagus due to sympathetic stimulation, but no change in the tonus of the musculature in the proximal portion. Contraction of the striated musculature of the esophagus elicited by vagus stimulation, according to Knight, is augmented by simultaneous sympathetic stimulation. The data available do not indicate an effective rôle of the sympathetic nerves.

Efferent stimulation of a single vagus branch to the esophagus elicits a purely segmental contraction. A peristaltic wave which is propagated along the esophagus cannot be initiated by efferent stimulation of the esophagus at any given point. The esophagus differs in this respect from the lower divisions of the digestive tube. Stimulation of the central end of the divided vagus, while the other vagus is intact, results in contraction along the entire esophagus. This in turn stimulates the afferent vagus endings throughout the esophagus, thus sending afferent impulses upward which activate the efferent neurons of the intact vagus and result in still further contraction of the entire esophageal musculature.

Peristalsis in the esophagus, like the swallowing reflex, is mediated through extrinsic nerves. Mosso (1876) showed that transection of the esophagus or even resection of entire segments does not prevent peristalsis if only the nerve supply to the several pieces remains intact. Meltzer (1906) also observed the propagation of peristaltic waves along the esophagus in the rabbit following its transection at several levels. He noted, however, that when the animal was under deep anesthesia, a peristaltic wave initiated in one segment stopped at the lower border of that segment and did not pass on to the next. A foreign body introduced into the esophagus results in a peristaltic wave beginning above the point of stimulation; consequently, if the primary reflex initiated at the beginning of the swallowing act succeeds only in forcing a bolus of food into the upper part of the esophagus, the bolus itself causes a series of reflex contractions, by local stimulation of the sensory fibers, which tend to move the bolus downward. This does not occur following section of the vagi, again showing that the peristaltic reflex is mediated through extrinsic nerves.

The orderly sequence of the movements involved in the swallowing reflex and esophageal peristalsis is dependent on a center in the medulla oblongata (deglutition center), located lateral to the ala cinerea and just above it, which probably involves portions of the tractus solitarius and the nucleus ambiguus. Whether it consists of a definite group of cells which send their axons directly to the motor nuclei of the several efferent nerves concerned is not definitely known. The close coordination of the swallowing reflex and respiratory movements suggests that the deglutition center is intimately associated with the respiratory center. Respiration is always inhibited during deglutition.

The swallowing reaction and esophageal peristalsis also are affected by psychic influences. Strong emotional disturbances, *e g*, joy, anger or fright, not uncommonly are accompanied by spasm of the pharynx and

esophagus which may temporarily render the swallowing reaction impossible. Hysterical individuals not infrequently complain of sensory disturbances in the esophagus which undoubtedly are associated with disturbances in its motor activity.

An essential rôle of the intrinsic neurons in the swallowing reflex or esophageal peristalsis has not been demonstrated. Rhythmic contractions of isolated pieces of the esophagus have been observed, but this does not prove independent functional activity on the part of the intrinsic nerves. Section of the vagus fibers which supply the lower portion of the esophagus and the cardia results in spastic contraction of the cardiac sphincter. Bilateral vagotomy at a somewhat higher level results in dilatation of the distal portion of the esophagus and contraction of the cardia (Knight, 1934). This condition subsides after a few days and the parts involved resume functional activity which continues in an apparently normal manner. This suggests that tonus and single contractions, at least in the lower portion of the esophagus, are influenced by the intrinsic nervous mechanism, although it has not been demonstrated that any single reaction involving the esophageal musculature is mediated solely through its intrinsic nerves.

Cardiac Sphincter.—The circular muscle is somewhat thickened at the cardiac orifice of the stomach and acts as a sphincter. Its innervation includes both vagus and sympathetic fibers and the intrinsic nervous mechanism, particularly the myenteric plexus. The sympathetic fibers involved are derived mainly from the celiac plexus; the corresponding preganglionic fibers are components of the greater splanchnic nerve.

The results of experiments involving stimulation of the vagus and sympathetic fibers to the cardiac sphincter are not all in full accord, due in part to differences in the innervation of this muscle in the various experimental animals and other variable factors. The interpretation of these results is beset by still further difficulties due to the fact that the fibers supplying the sphincter cannot be stimulated without at the same time stimulating vasomotor and secretory fibers and perhaps the adrenals. The stage of anesthesia, furthermore, plays an important role. All these factors complicate the result of the experiment and cannot be disregarded.

The vagus, like the sympathetic supply to the cardiac sphincter, exerts both motor and inhibitory effects. If the muscle is relaxed or in a state of low tonus, vagus stimulation results in contraction; if the sphincter is closed, it results in relaxation, thus opening the cardiac orifice (Carlson, 1922). In Carlson's experiments, splanchnic stimulation resulted only in motor action of the cardiac sphincter in the dog, only in inhibitory action in the rabbit, and in both motor and inhibitory action in the cat. Knight (1934) reported only contraction of the sphincter in the cat in response to stimulation of fibers from the celiac ganglia, and its relaxation following bilateral sympathectomy. In experiments reported by Ferguson (1936), bilateral vagotomy in the monkey resulted in persistent cardiospasm. Brucke and Stern (1938) also reported cardiospasm due to bilateral vagotomy which was abolished by atropine and adrenin but exaggerated by eserine, acetylcholine and pilocarpine. That relaxation of the cardiac sphincter is not the result of mechanical pressure due to contraction of the esophagus which tends to force the esophageal content into the stomach was clearly shown by Langley (1899) who demonstrated, by the use of a water manometer, that following vagus stimulation liquids flow from

the esophagus into the stomach under pressure conditions which are inadequate to bring about mechanical opening of the cardiac orifice. The peristaltic wave passing along the esophagus is preceded, at least in the lower part of the esophagus, by a wave of inhibition or relaxation which also affects the cardiac sphincter and the adjacent gastric musculature. In this manner, the way is opened for the bolus, so that the peristaltic contraction may force it through the cardiac orifice without much resistance. By the use of the esophagoscope Mikulicz (1903) showed that the cardiac sphincter remained closed until the tube of the instrument approached to within a few centimeters of the cardia but as the tube approached more closely the sphincter gradually opened. This reflex inhibition apparently was elicited by stimulation of afferent fibers in the mucosa of the lower portion of the esophagus. Schiff (1926) maintained that the reflexes involved in this reaction pass through the central nervous system and that both the afferent and efferent neurons involved are components of the vagus nerves.

Following the passage of a bolus of food into the stomach, the cardiac sphincter again closes until another peristaltic wave passing down the esophagus approaches. According to Cannon (1911), the tonic contraction of the cardiac sphincter, which develops when the stomach contains food, is maintained through reflex activity of the intrinsic plexus initiated by the stimulating effect of the acid in the gastric secretion. Carlson (1922) pointed out that the tonus of the cardiac sphincter is high while gastric digestion is in progress. According to his findings, "this hypertonus persists after removing the food from the stomach, washing the stomach cavity with water at body temperature, or rendering the stomach content alkaline. 0.4 per cent HCl in the stomach does not increase the tonus of the cardia parallel to that found in the digesting stomach." He also observed that the tonus of the cardiac sphincter is diminished under light but increased under deep anesthesia.

Stomach.—Although the musculature of the stomach is composed exclusively of smooth muscle fibers, it is more complex than that of the other divisions of the digestive tube. Its motor activities also are correspondingly complex. The gastric musculature, furthermore, under the influence of the intrinsic nervous mechanism possesses the capacity to undergo reflex adjustment to the changing volume of the gastric content without exhibiting appreciable changes in tonus (Cannon, 1911). The pressure within the stomach is not increased by an increase in the volume of the stomach content, nor does an increase in the volume of the stomach increase the intra-abdominal pressure (Burns, 1920). The abdominal muscles undergo reflex adjustment to changes in the gastric content. The latter reaction is a reflex phenomenon mediated through reflex arcs whose afferent limbs are components of the splanchnic nerves and whose efferent limbs are components of the spinal nerves through which the abdominal muscles are supplied.

Gastric motility is not interrupted following bilateral section of vagus and splanchnic nerves. Under proper conditions, activity may still be observed in the excised stomach. With respect to its motor activities, therefore, the stomach may be regarded as an automatic organ. Its automatic activities are elicited by stimuli which arise within itself and appear to be carried out through its intrinsic nervous mechanism. These activities

normally are regulated and controlled through the vagus and splanchnic nerves

In general, vagus stimulation augments but, under certain conditions, it inhibits gastric motility Gastric inhibition in response to vagus stimulation was observed by Doyon as early as 1894 Langley (1898) also observed this phenomenon and concluded that the vagus supply to the stomach includes some fibers whose action is inhibitory Meltzer and Auer (1906) associated gastric inhibition in response to electrical stimulation of the vagus with the strength of the current used Klee (1912, 1919) observed only motor effects of vagus stimulation on the stomach but, in his experiments, moderate stimulation resulted in augmentation of the motor movements whereas strong stimulation resulted in tonic contraction of the gastric musculature Most of the more recent investigators who have studied the effects of vagus stimulation on the stomach, including Carlson and Luckhardt (1920) Carlson Boyd and Pearcey (1922), McCrea, McSwiney and Stopford (1925), Schilf (1926), Laughton (1929), Patterson and Rubright (1934) and Barron (1937) sometimes observed inhibitory effects, although the more common effect is augmentation of gastric motility The results obtained by certain of these investigators, particularly McCrea McSwiney and Stopford, Laughton and Patterson and Rubright, indicate that vagus stimulation may either initiate gastric motility, if the stomach is in a state of low tonus or augment and sometimes accelerate motility if movements are present On the contrary if the gastric musculature is in a state of high tonus, motility is inhibited and the musculature is relaxed by vagus stimulation Veach (1925) reported that stimulation of the distal portion of the vagus after section, with relatively low frequencies or intensities results in gastric excitation, whereas stimulation with considerably higher frequencies or intensities results in gastric inhibition McSwiney and Wadge (1928) failed to corroborate this finding of Veach but reported that, in conditions of low tonus, stimulation of the vagus with low or high frequencies or intensities results in contraction of the gastric musculature and an increase in its tonus, whereas in conditions of high tonus stimulation of the vagus with low or high frequencies or intensities results in gastric inhibition Veach, Schwartz and Weinstein (1930) obtained both motor and inhibitory effects by varying the frequency of the stimulating current independently of the initial tonic condition of the gastric musculature Brown and Gray (1931), using the decapitate cat, found that the inhibitory effect of vagus stimulation on the stomach is abolished following injection of sodium amytal In view of all the data available, the initial tonic state of the gastric musculature seems to play a more important role than the frequency or strength of the stimulating current in determining the effect on the stomach of vagus stimulation

The left vagus exerts a greater influence on gastric motility than the right (Laughton, 1929, Barron, 1937) McCrea *et al* (1926) and McSwiney (1931) observed no effect of unilateral vagotomy on the stomach Barron (1937), on the contrary, reported a definite decrease in the duration of periods of gastric motility associated with a corresponding increase in the duration of periods of quiescence following section of the left vagus Bilateral vagotomy results in a decrease in gastric tonicity and lengthening of the emptying time (Meek and Herrin, 1934, Ferguson, 1936)

Splanchnic stimulation commonly results in inhibition of gastric motility and relaxation of the gastric musculature. Not a few investigators, including Morat (1893), Doyon (1894), Carlson, Boyd and Pearcey (1922), Thomas and Wheelon (1922), Nulf (1925), Veach (1925) and Barron (1939) also observed an opposite effect. McCrea and McSwiney (1928) reported that stimulation of the peripheral portion of either splanchnic nerve after section results in an increase in the tonus of the gastric musculature if it were in an initial state of low tonus but in inhibition of motility and relaxation of the gastric musculature if it were in an initial state of high tonus. Brown, McSwiney and Wadge (1930), working with spinal and decerebrate cats and dogs with the stomach divided at the incisura, found that the effect of splanchnic stimulation on the stomach is determined at least in part by the type of stimulation employed. In their experiments, stimulation with a frequency of 1 per second brought about contraction, while stimulation with a tetanizing current resulted in relaxation of the gastric musculature. The antrum did not respond in the same manner, but was always inhibited in the cat and usually in the dog by splanchnic stimulation regardless of the type employed. Brown and McSwiney (1932) reported reversal of the effect of splanchnic stimulation on the stomach following anesthesia with luminal or injection of this substance into a spinal animal. They advanced the opinion that the reversed effect of splanchnic stimulation on the stomach, following the administration of luminal, is due to the depressing effect of this substance on the rate of production or the action of the hormonal substance liberated at the periphery as a result of sympathetic stimulation.

The stomach also responds reflexly to stimulation of somatic afferent nerves. In the experiments reported by Patterson and Rubright (1934) stimulation of the sciatic nerve in the monkey resulted in reflex inhibition of the gastric musculature when it was in a preëxisting hypertonic state, and in contraction or augmentation of the tonus when it was in a preëxisting hypotonic state. Compression of the eyeball also elicited reflex changes in the gastric musculature, depending on the preëxisting state of tonicity. They advanced the opinion that stimulation of any afferent nerve may exert an influence on the stomach through reflex mechanisms involving efferent components of both the vagus and splanchnic nerves and that the nature of the response is determined by the preëxisting state of tonicity of the gastric neuromuscular mechanism.

In view of all the data available, it must be conceded that the initial state of tonicity of the gastric musculature is an important factor in determining the effect either of direct or reflex stimulation of the stomach through either the vagus or splanchnic nerves. The concentration of adrenin and other humoral substances in the circulating blood and the substances liberated as a result of nerve stimulation constitute additional factors. Under certain conditions, the type of stimulation employed also seems to play a rôle in determining the nature of the response.

Splanchnic resection results in marked alterations in gastric motility. McCrea (1925) reported increased gastric peristalsis and a more tubular form of the stomach following this operation. The emptying time of the stomach also was markedly decreased. In human subjects Barron (1937) observed short periods of motility alternating with short periods of quiescence eight to ten days after unilateral splanchnic resection. Subse-

quently the periods of gastric activity became greatly lengthened and the amplitude of the contractions increased The effects of bilateral splanchnic resection were essentially similar to those of unilateral resection In one patient studied seven months after this operation the exaggerated gastric activity still persisted Unilateral splanchnic resection in Barron's experience, resulted in no marked change in the average rate of gastric emptying but the average emptying time was markedly reduced following bilateral splanchnic resection

Pyloric Sphincter — According to most observers the pyloric sphincter responds both to vagus and splanchnic stimulation in essentially the same manner as the gastric musculature Certain investigators, particularly Smith (1918), Klee (1919) and Koennecke (1922) have pointed out that splanchnic stimulation not uncommonly results in contraction of this muscle According to Thomas and Wheelon (1922) the effect of stimulation of the extrinsic nerves is the same on the motility of the pyloric sphincter as on that of the pyloric antrum This finding supports the theory that the pyloric sphincter is not a separate functional entity but that the pyloric antrum and sphincter constitute a functional unit and have a common nerve supply According to the results of their experiments, the function of both the vagus and splanchnic fibers supplying the pyloric sphincter is mainly motor Both nerves also include fibers which are inhibitory to the pyloric sphincter but these are more abundant in the splanchnic than in the vagus The initial tonic state of the pyloric sphincter also is a factor in determining its response both to vagus and splanchnic stimulation

The effects of artificial stimulation of the extrinsic nerves in question indicate the functional character of their efferent fibers but afford no adequate concept of the normal functioning of the pylorus When food is taken into the stomach, contractions are initiated about the middle of the organ and advance toward the pylorus As digestion progresses, these contractions become stronger and, at certain irregular intervals but not with each contraction wave, the pylorus opens as a wave of contraction approaches Klee (1912), who by the use of the fluoroscope, observed the movements of the stomach elicited by vagus stimulation while it contained a barium meal carefully described these movements According to his observations, the pyloric sphincter relaxes quite suddenly shortly before a wave of contraction reaches the pylorus, allowing the entire food mass which was separated from the rest of the stomach content by the contraction in question, to pass into the duodenum He never observed opening of the pylorus unless the approaching wave of contraction carried a mass of the stomach content before it It appears therefore, that the relaxation of the pyloric sphincter was not the direct result of vagus stimulation but the result of the peristaltic contraction which carried a mass of the stomach content into the pyloric region When a considerable mass of the stomach content had passed into the duodenum and still remained there the pylorus did not open at the approach of a peristaltic wave of contraction which carried an adequate volume of the stomach content before it regardless of the strength of the peristaltic contraction The normal functioning of the pyloric sphincter appears to be controlled by closely coordinated reflex mechanisms which involve both the stomach and the duodenum

Retention of the gastric content in the stomach until it has reached a satisfactory state of digestion depends on impulses arising within the stomach The rate of discharge from the stomach is adapted to the functional capacity of the intestine by reflex activity initiated within the intestine (Thomas, 1931) The reflex activity involved in gastric evacuation is mediated mainly through the myenteric plexus and the vagus nerves The myenteric reflexes are concerned mainly with regulation of the tonus of the pyloric sphincter Reflexes through the vagi exert an inhibitory influence on the pyloric *portion of* the stomach which *tends to* decrease the motility of the pyloric antrum, including the sphincter The threshold of stimulation of the vagus reflex mechanism is lower than that of the myenteric, consequently, the former usually dominate the latter, particularly in the chemical regulation of the discharge of the gastric contents into the intestine

Among the intra intestinal stimuli which affect gastric motility are mechanical distention, chemical irritation acid hypotonic and hypertonic solutions, fat and the products of protein and carbohydrate digestion The regulation of gastric evacuation, as outlined by Thomas (1939), may be explained as follows The material discharged from the stomach into the duodenum, after gastric digestion has been going on for some time normally includes HCl, proteoses and peptones, fat and the products of carbohydrate digestion One or more of these substances soon accumulates in the intestine in sufficient concentration to stimulate the appropriate receptors for enterogastric reflex activity or initiate the liberation of enterogastrone The tonus of the gastric musculature and the intragastric pressure consequently, are diminished and peristalsis grows weaker, so that the discharge of gastric contents into the duodenum proceeds at a slower rate As soon as the gastric discharge fails to keep pace with intestinal digestion and absorption *gastric motor activity may* be expected to *increase* As soon as the stimulating materials are again present in the intestine in adequate concentration gastric motility is again reflexly inhibited When once the rate of emptying is adjusted so that the concentration of the gastro-inhibitory substances in the intestine is maintained at the threshold level or a little above it, gastric activity probably continues with little further change The initial discharge of stomach contents into the intestine following the ingestion of food undoubtedly can be explained most satisfactorily as due to the gastric "motor drive" which is constantly present during digestion The regulation of gastric evacuation therefore tends to prevent overloading of the intestine, which is accomplished mainly through gastro-inhibitory reflexes and humoral influences initiated within the intestine by the presence of food materials and the products of their digestion Since the changes in the tonus of the pyloric sphincter correspond to those of the pyloric antrum, it constantly tends to resist the discharge of the gastric contents into the duodenum and blocks the passage of solid particles It also tends to limit regurgitation by contracting when the duodenum contracts

Hunger Contractions —In man the empty stomach exhibits movements of two types (*a*) rhythmic tonus changes of the fundus and corpus, and (*b*) hunger contractions The former usually are not very marked The latter are powerful waves which arise at the cardia and traverse the entire stomach Hunger contractions are initiated about three hours after a

meal *i e* when the stomach is nearly empty They are superimposed on the tonus rhythm and occur in series (hunger periods) separated by intervals in which the stomach exhibits no motility except the tonus rhythm Hunger periods usually last from thirty to forty-five minutes, but may be as brief as six minutes or as long as one and one-half hours The intervals of quiescence commonly last from one-half to two and one-half hours Hunger contractions commonly give rise to a sensation of hunger with which may be associated actual discomfort or pain (hunger pang) During extended periods of fasting the hunger contractions are not diminished but the hunger pangs and the general sensation of hunger become less intense after the third day Hunger contractions also may be inhibited reflexly by various means *e g* strenuous muscular exercise taking a quantity of water into the stomach application of cold to the surface of the body, compression of the abdomen, etc (Carlson 1916)

Dextrose solutions introduced into the stomach have a marked inhibitory effect on hunger contractions In experiments on dogs reported by Manville and Munroe (1937) hunger contractions were effectively inhibited by 10 to 25 per cent solutions of dextrose introduced into the empty stomach through an artificial fistula Gastric motility induced by pilocarpine and insulin was inhibited by the same means

The Nervous Mechanism of Vomiting —Vomiting is a reflex reaction which borders on the pathological and not infrequently serves the useful purpose of ridding the stomach of harmful substances The role of the stomach in this reaction consists in tonic contraction of the pylorus and pyloric antrum inhibition of fundic peristalsis and relaxation of the cardia and cardiac sphincter The gastric content is expelled through the esophagus by the sudden and simultaneous contraction of the diaphragm and abdominal muscles (Cannon 1911) Vomiting commonly is caused by abnormal stimulation of the terminations of afferent vagus fibers in the stomach Goldberg (1931) reported reflex vomiting in the dog induced by distending an isolated pyloric pouch In this instance the afferent impulses were conducted solely by vagus fibers Vomiting also may be elicited by artificial stimulation of afferent vagus fibers and other sensory nerves Not infrequently it is caused by disturbances of the urogenital apparatus, liver and other visceral organs It may also be caused by disagreeable emotions and disturbances of equilibrium The afferent impulses involved reach the medulla regardless of whether they are conducted by the vagus or other afferent nerves The efferent impulses, through which contraction of the pyloric sphincter and antrum is brought about are conducted by the vagus those which bring about inhibition of the fundus and relaxation of the cardia by the splanchnic nerves The contraction of the diaphragm and abdominal muscles is brought about by impulses conducted by the phrenic and lower thoracic nerves The coordinated impulses which are sent out to the various muscles involved arise in the medulla A medullary area in the vicinity of the motor nucleus of the vagus and close to the respiratory center, but distinct from the latter, probably includes a vomiting center, since vomiting cannot be carried out following destruction of this area

Vomiting not infrequently is a symptom of disease or injury of the brain (meningitis brain tumor, etc) which brings about an increase in intracranial pressure In this condition, the direct cause of vomiting

probably is the increased hydrostatic pressure in the fourth ventricle which stimulates the vagus nuclei directly. Localized injuries of the brain and spinal cord commonly are not accompanied by vomiting.

Nervous Regulation of Gastric Secretion.—Gastric secretion has long been known to be regulated in part by nervous influences, but knowledge of the specific effects of the various components of the gastric nerve supply on secretory activity has awaited the results of relatively recent investigations. The findings of Bickel (1925) and his collaborators support the following assumptions. The chief and parietal gland cells in the fundus are innervated by both parasympathetic and sympathetic fibers which excite and sympathetic fibers which inhibit secretory activity. The parasympathetic fibers exert the major influence in the secretion of water and hydrochloric acid in this part of the stomach, while the sympathetic secretory fibers play but a secondary role in this function. The sympathetic secretory fibers exert the major influence in the secretion of enzymes, while the parasympathetic fibers play but a secondary role in this function. According to Baxter (1932), sympathetic stimulation also increases the secretion of mucoid material. The sympathetic inhibitory fibers inhibit all secretory activity. The chief cells in the pyloric region are innervated only by sympathetic fibers, some of which excite and others inhibit secretion. In this part of the stomach, the sympathetic secretory fibers excite both the secretion of enzymes and water, but water is secreted by the pyloric glands only in relatively small quantities.

In experiments carried out on frogs, Friedman (1937) found that mechanical stimulation of the gastric mucosa by inert substances elicited secretion of pepsin by the esophageal glands and of both acid and pepsin by the gastric glands through reflex activity mediated by the splanchnic nerves. Secretion of pepsin by the esophageal glands was also stimulated by adrenin but not by pilocarpine or acetylcholine. Secretion of both acid and pepsin in the stomach was stimulated by adrenin but not by pilocarpine or acetylcholine. Histamine stimulated the secretion of pepsin by the esophageal glands but only of acid and not of pepsin by the gastric glands. According to Jennings and Florey (1941), the secretory activity of the cardiac and pyloric mucous glands and the mucous neck cells of the fundic glands in mammals is controlled through the vagi, but these nerves exert no influence on the surface epithelial cells in the stomach.

According to de Vecchi (1927), section of the sympathetic nerves in animals was followed by a marked increase, and section of branches of the vagi by a marked diminution in the quantity of hydrochloric acid secreted in the stomach. Section of both sympathetic and vagus branches was followed by slight diminution in the quantity of hydrochloric acid secreted. He also cited two clinical cases in which resection of the vagus branches along the lesser curvature of the stomach and the sympathetic nerves approaching the pyloric region was followed by diminution of hydrochloric acid secretion, which was still appreciable after one and a half years. According to Friedenwald and Feldman (1932), the changes in gastric secretion produced by section of one or both vagus nerves are relatively slight and transient. Shapiro and Berg (1932) also reported only a temporary reduction in gastric acidity which was followed by complete restoration of the secretory function, following subtotal gastrectomy combined with bilateral infraphrenic vagotomy in dogs. The

division of both vagi did not abolish the action of atropine on the gastric glands. In experiments reported by Brown (1933), extirpation of the sympathetic trunks and the celiac ganglia in cats resulted in no demonstrable change either in the free or the combined gastric acidity.

Although interruption of either the vagus or sympathetic nerves supplying the stomach, in most of the experiments cited above, was followed by no marked changes in gastric secretion, the results observed do not warrant the conclusion that gastric secretory activity is not subject to nervous influences. The assumptions that gastric hyperacidity commonly is associated with parasympathetic hyperirritability, and gastric hypoacidity with sympathetic hyperirritability are supported by ample experimental and clinical data. (See Chapter XX.) Winkler (1934) also advanced certain clinical data in support of the assumption that both hypo- and hyperactivity of the gastric glands, in certain cases, are associated with lesions of the nerves supplying the gastric mucosa.

Under normal physiologic conditions the secretory activity of the fundic glands ceases while the stomach is empty. The pyloric glands remain active, producing in small quantities an enzyme-containing secretion in which the pepsin must remain inactive due to the lack of hydrochloric acid unless hydrochloric acid is secreted in small quantities by the parietal cells. The inhibition of the fundic glands, according to Bickel, probably is due to inhibitory impulses of central nervous origin conducted by sympathetic fibers incorporated in the vagus nerve which probably are absent in the pyloric region. When food is taken into the mouth the stimulation of the sense organs involved and the accompanying psychophysiologic processes initiate strong reflex parasympathetic excitation in the presence of which the central inhibitory influences acting on the fundic glands gradually subside and these glands are thrown into secretory activity. As the food enters the stomach it stimulates the gastric mucosa directly, first in the fundus, then in the pyloric region, and somewhat later in the duodenum, giving rise to afferent impulses which are conducted by the general visceral afferents to the appropriate centers in the central nervous system. Both secretory and inhibitory impulses emanating from these centers are conducted back to the glands through visceral efferent conduction chains. As the process of digestion progresses the secretin produced by the active mucosa and the secretin-like substances contained in the food reach the intestine and, being absorbed, are added to the secretin already present in the blood. This in turn exerts an influence on the secretory activity of the gastric glands.

As the food passes into the intestine and the stomach once more becomes empty, both the reflex and humoral excitation of the gastric glands subsides and the central inhibitory impulses again gain the ascendency, the fundic glands become quiescent and the pyloric glands, in the absence of reflex inhibition, continue their normal secretory activity.

The chemical phase of gastric secretion, according to Babkin (1938), is regulated through (1) a hormonal substance, probably gastrin, which acts directly on the gastric glands, (2) certain food substances or products liberated by them, which stimulate the gastric glands after being absorbed in the intestine, and (3) certain absorbed products of digestion, as well as a hypoglycemic state of the blood, which exert a direct influence on the vagal centers.

The assumption that the acidity of the gastric secretion is regulated mainly by duodenal regurgitation and acid inhibition is supported by abundant experimental data, particularly those advanced by Wilhelmj and his collaborators (1936–1939). As summarized by Wilhelmj and Sachs (1939), the acidity of the gastric contents (cc. of acid secretion per 100 cc. of gastric contents) is controlled primarily by acid inhibition, the acidity of the total secretions entering the stomach primarily by duodenal regurgitation. The latter process may or may not influence the acidity of the gastric contents. These two mechanisms probably vary in relative importance in different normal subjects. Failure of one or the other in disease is theoretically possible. If, during normal acid inhibition, duodenal regurgitation did not occur, the secretory curve would show a high and maintained value for the acidity of the total secretions entering the stomach but a normal acidity value for the gastric contents. If, in the presence of normal duodenal regurgitation, acid inhibition should fail, the secretory curve would show normal acidity of the total secretions entering the stomach but a high value for the acidity of the gastric contents.

Gastric secretory activity may be modified by the administration of various pharmacologic agents. Ephedrine, a sympathomimetic substance, causes a distinct reduction in the total acidity and the free HCl in the gastric juice (Rafferty *et al.*, 1937). Acetyl-beta-methylcholine chloride (Schnedorf and Ivy, 1937) and acetylcholine (Necheles *et al.*, 1938), parasympathomimetic substances, stimulate the production of free acid. In the experiments of Necheles *et al.*, acetylcholine caused an increase in the acid, volume and pepsin secretion in a Heidenhain pouch. Acetylcholine and histamine were found to be synergistic in relation to gastric secretion. Acetyl-beta-methylcholine chloride also caused an increase in the volume, acid and pepsin of the gastric secretion of normal subjects. Ergotamine tartrate in large doses diminishes the acid secretory response to histamine (Atkinson and Ivy, 1937). Dextrose introduced into the stomach tends to inhibit the gastric secretory activity caused by histamine, pilocarpine or insulin (Manville and Munroe, 1937). Centrally acting emetics, *e. g.*, apomorphine, emetine and quinine, in subemetic doses decrease the total acid output, but a decrease in the titratable acidity requires emetic doses (Atkinson and Ivy, 1937). The common finding that olive oil in the duodenum causes inhibition of gastric secretory activity which is followed by stimulation has been confirmed by Shay, Gershon-Cohen and Fels (1939).

Data reported by Bucher (1940) seem to indicate that histamine causes an increase in the production of pepsin as well as in that of hydrochloric acid. In her experiments, in which small constant doses of histamine were given every ten minutes for five to eight hours, the hourly output of pepsin in the gastric juice secreted by a pouch of the entire stomach following vagotomy was increased and constant. Data advanced by Ivy and Bachrach (1940) also seem to support the assumption that the excessive secretion of gastric juice associated with inflammation or ulceration in the intestine may be due to the stimulating effect of the histamine liberated at the site of the lesion. In their experimental animals, atropine depressed the gastric secretion after a meal to only about the same extent as it did the secretory response to histamine.

Intestine.—In general, vagus stimulation results in excitation of the intestinal musculature as far as it is supplied by vagus fibers, whereas stimulation of the splanchnic or hypogastric nerves results in inhibition of the intestinal musculature. In some instances stimulation either of the vagus or sympathetic nerves produces the reverse effect. Section of the vagus nerves in general results in decreased intestinal motility, sympathectomy in increased motility. In experiments reported by Sealy and Wichter (1936), sympathetic denervation of the intestine and adrenals in the cat resulted in a reduction of 52 per cent in the average time required for barium sulphate suspension to reach the cecum from the stomach. Stimulation of the sacral parasympathetic nerves commonly elicits contraction of the musculature of the colon, rectum and anal canal. The ileocolic sphincter apparently is supplied mainly by sympathetic fibers. It commonly contracts in response to splanchnic stimulation, and is not affected by stimulation either of the vagus or sacral parasympathetic nerves. In experiments reported by Ludány and Jourdan (1936), the intestinal villi relaxed in response to vagus stimulation, whereas splanchnic stimulation elicited contraction of the villi and inhibition of their motility. Vagus stimulation, therefore, increases the area of the intestinal epithelium, whereas splanchnic stimulation decreases it.

The reversed action of vagus and splanchnic stimulation on the intestinal musculature has been explained on the assumption that the vagus nerves include some inhibitory fibers and the sympathetic nerves some motor fibers to the intestine (Bayliss and Starling, 1913). The results of certain investigations strongly suggest that the specific effect either of vagus or sympathetic stimulation on the intestine is determined at least in part by the initial tonic state of its musculature. According to Carlson (1930), stimulation of the peripheral ends of the hypogastric nerves, the efferent fibers of which all probably are sympathetic, elicits contraction of both muscle layers of the large intestine if the musculature is relatively atonic, and inhibition of both layers if the muscles are active and in a fair degree of tonus.

In Carlson's (1930) experiments, stimulation of the sacral parasympathetic nerves produced only a motor effect on both muscle layers in the large intestine. According to Learmonth and Markowitz (1930), the lumbar colonic nerves exert a constant inhibitory influence on the distal parts of the colon. Section of these nerves, in their experiments, resulted in an immediate increase in intracolonic pressure and sometimes in an increase in the amplitude of the colonic contractions. In experiments reported by Wells, Mercer, Gray and Ivy (1942) electrical stimulation of the pelvic nerves elicited contraction of both the longitudinal and circular muscles of the descending colon. Impulses conducted by these nerves also influenced the musculature of the proximal portion of the colon via enteric conduction pathways. Electrical stimulation of the vagi elicited no response in the colon of the dog, but sometimes elicited weak and inconstant contractions in part of the cecum in the pig and the monkey. Electrical stimulation of the celiac root of the inferior mesenteric plexus elicited inconstant circular contraction of the colonic musculature limited to the descending colon. Stimulation of the hypogastric nerves elicited inconstant circular contraction limited to the distal portion of the descending colon.

A dual contractile and tonic mechanism in the colon could not be demonstrated

In a study of the duodenal reactions elicited by various pharmacologic agents, Camp (1936) obtained certain data which support the assumption that duodenal tonus and activity involves a series of oxidation and reduction processes which occur normally in the cells As oxidation becomes predominant, potassium enters the cells, as reduction gains the ascendency potassium leaves the cells An excess of potassium within the cell results in contraction, on the cell surface, whether derived from within the cell or applied from without, it results in relaxation

Distention of the jejunum in dogs, according to Youmans, Meek and Herrin (1938), results in inhibition of motility of all types and diminution of the tonus of its undistended parts in both directions from the site of the distention The degree of inhibition is determined by the rapidity of the distention and the final pressure attained A weaker inhibitory response is elicited by distention following section of the extrinsic nerves but destruction of the enteric connections while the extrinsic nerves are intact does not alter the response The inhibition caused by distention of the jejunum therefore, seems to be mediated primarily through extrinsic nerves The degree of motility observed at the site of a distention, according to Youmans (1940), depends in part on the balance between the reflex inhibitory and the direct stimulatory effects In the denervated intestine distention acts as a direct stimulus to the smooth muscle

In experiments reported by Pei and Long (1942), stimulation of a loop of the small intestine by pressure, heat, mechanical injury or electrical stimulation of its afferent nerves elicited inhibition of the entire intestine The reflexes involved are mediated through spinal cord centers in the eighth thoracic to the first lumbar segments inclusive The afferent fibers do not cross to the opposite side and the reflex connections are effected in the segments in which they enter the cord

The sensitivity of the dog's jejunal musculature to adrenin, according to Youmans Karstens and Aumann (1942), is not materially altered by bilateral vagotomy Bilateral section of the preganglionic sympathetic nerves either has no effect or results in less than a two-fold increase in the sensitivity of this musculature to adrenin Section of the mesenteric nerves to a given intestinal segment renders the musculature of this segment several times more sensitive to adrenin than that of other segments with the nerves intact

In an experimental study of gastro-intestinal motility in dogs, Raiford and Mulinos (1936) found that the jejunum is more irritable and responds more quickly to stimulation than other parts of the small intestine Its minor rhythmic contractions at a definite oscillatory frequency also persist longer and the contractions of the circular muscle are predominant These facts are significant in relation to the function of the jejunum in the propulsion of the intestinal contents The ileum is not only less irritable but its contractions exhibit no rhythmic oscillations and the amplitudes of the contractions of both the longitudinal and circular muscles are smaller The colon exhibits the most powerful contractions, and those of either muscle layer may predominate depending on the direction of the stimulus This activity, according to these investigators, is mediated mainly through myenteric reflex mechanisms

In studies carried out on exteriorized loops of intestine, in continuity and covered with a tube of skin, Douglas and Mann (1939, 1940) confirmed the current concepts of the gradient theory and the constancy of the rate of contraction in any given segment. They observed increased motility in the small intestine following ingestion of food which occurred earlier in the jejunum than in the ileum. This response was not abolished by bilateral vagotomy. It failed to occur following transection of the intestine, although the extrinsic nerves remained intact but it did occur distal to the section following re-anastomosis of the intestine in such a way as to prevent immediate union of the muscular coats and the enteric plexuses. This response to food was also observed in the distal portion of the colon but not in its proximal portion. The response in the small intestine was as constant when the animal was fed through a fistula as when food was taken by mouth. Welch (1937) described reflex activity of the colon in man in response to feeding by mouth which did not occur when food was given through a gastric fistula. He therefore regarded the reaction as an appetite or taste reflex and not a gastrocolic reflex. He also described responses of the colonic musculature to psychic stimulation and to impulses arising in adjacent viscera.

In a series of experiments carried out on dogs Lawson and Templeton (1932) observed that peristalsis in the proximal portion of the colon is accompanied by rhythmic pulsations and shortening of the distal segments of the large intestine. The shortenings stand in the same reciprocal relationship to the rhythmic pulsations of these segments as does the proximal peristalsis. The reciprocal relationship between the longitudinal and circular activity of the distal segments of the large intestine is most marked in the region of the anal sphincters, *i. e.* the region in which circular activity is greatest. Whenever peristalsis is present in the proximal portions of the colon, longitudinal activity of the distal segments of the large intestine runs parallel with it, but there is no corresponding relationship between longitudinal activity of the distal segments and other types of activity in the proximal colon. The reciprocal relationship between the activity of the proximal and distal portions observed in the intact large intestine, is preserved after transection in the region of the splenic flexure.

The anal canal is guarded by an internal and an external sphincter muscle. The external sphincter ani is composed of striated muscle and is subject to voluntary control within certain limits. It is supplied by the inferior hemorrhoidal branch of the pudendal nerve. The internal sphincter ani is composed of smooth muscle. Like the rest of the smooth musculature of the anal canal, it is supplied with sympathetic and parasympathetic nerves. Its sympathetic supply, according to Learmonth and Markowitz (1929), includes both motor and inhibitory fibers. Both the internal and external sphincters normally are in tonus, but the force of the tonic contraction of the external sphincter normally is greater than that of the internal sphincter. A certain degree of reflex interdependence of the internal and external sphincters also has been recognized (Garry, 1933). The effects on the internal sphincter ani of artificial stimulation of its sympathetic and parasympathetic innervation seem to vary in different animals. Mechanical irritation or electrical stimulation of the anal sphincter area in the dog, according to Lawson and Templeton (1931), results in increased tonus and activity in this area and possibly in the

adjacent segments and depression of the tonus and activity of the proximal portion of the colon Electrical stimulation of other areas of the distal colon is less effective both locally and on the proximal colon Moderate distention of either the proximal or distal colon has no appreciable effect except for a slight local augmentation of activity without increase in tonus

Normal defecation is in part a voluntary and in part an involuntary act Under certain conditions defecation may be carried out as a pure reflex The defecation reflex involves peristaltic contractions of the rectum or the entire colon together with inhibition of the anal sphincters This reflex normally is excited by the entrance of feces into the rectum (Caoooo 1911, Muller, 1911) Defecation may be inhibited voluntarily by contraction of the muscles of the pelvic floor Contraction of these muscles gives rise to afferent impulses which bring about reflex inhibition of the movements of the colon and rectum

Defecation normally is mediated through reflex centers in the upper lumbar and sacral segments of the spinal cord Destruction of these centers results in a temporary diarrhea lasting for several days This is followed by normal evacuation of the large intestine at the usual intervals (Goltz 1896) The results of destruction of the spinal cord vary somewhat in different animals (Elliott and Barclay-Smith 1904) but, when free from both motor and inhibitory control through the spinal cord, the local nervous mechanism seems to have the capacity to regulate and control the defecation reflex (Muller, 1911) The pelvic nerves undoubtedly play a major role in normal defecation In experiments reported by Trumble (1935) stimulation of these nerves usually resulted in immediate shortening of the colon and drawing it distalward This reaction is followed after an interval by contraction of the circular muscle beginning in the upper part of the distal colon and spreading distalward, driving feces before it This wave of contraction is sometimes followed by other waves of like nature When the pelvic nerves are divided peristaltic action of the colon is released and its storage function is temporarily abolished

In a study of automatic defecation following destructive lesions of the sacral innervation of the rectum and anus in man Denny-Brown and Robertson (1935) found that contraction of the rectum is accompanied by reciprocal relaxation of the anal sphincter This reciprocal reaction is mediated through intrinsic reflex mechanisms which are activated by tension on the rectal wall These mechanisms may be depressed by spinal shock for a brief interval during which passive distention of the rectum elicits only slight relaxation of the anal sphincter Postural tonus of the rectum and anal sphincter is a reaction to passive tension of the muscle involved Rapidly increasing tension of this musculature causes tonic contraction to give way to phasic contractions Tension, therefore is also the stimulus for phasic movement If delivery of fecal material from the colon is adequate the mechanism of defecation depends primarily on the reaction of the rectum to distention The inefficiency of defecation following transverse spinal lesions is due to the relatively small force of rectal contraction even after recovery of the automatic reflex function

The application of centrally acting evacuants to the floor of the fourth ventricle in the dog according to Koppanyi (1930), may elicit straining and defecation which may be abolished by the application of morphine sulphate or lesions in the same area This suggests the existence of a

center in the medulla oblongata which may exert an influence on the mechanisms of defecation. Certain data reported by Langworthy and Rosenberg (1939) support the assumption that the tonus of the rectal musculature also is influenced through a center in the mid-brain.

Reflexes mediated through the extrinsic nerves play only a minor role in the control of intestinal activity, yet reflex inhibition of the movements of the small intestine may be brought about by stimulation of any afferent nerve. The reflexes involved are mediated through centers in the medulla and spinal cord and are carried out through the splanchnic nerves (Hotz, 1909). According to Lehmann (1913) inhibition is the only effect on the small intestine which can be brought about by stimulation of afferent nerves. On the other hand, afferent stimulation of the vagus and somatic nerves exerts a motor influence on the large intestine while afferent stimulation of splanchnic, hypogastric and visceral sacral nerves exerts mainly an inhibitory influence on this division of the digestive tube. Lehmann further pointed out that reflexes affecting the intestine which are elicited by stimulation of the vagus and somatic afferent nerves are mediated through centers in the medulla while those elicited by afferent stimulation of the splanchnic, hypogastric and visceral sacral nerves are mediated through centers in the spinal cord.

Physiologic Relationships of the Enteric Plexuses.—Section of extrinsic nerves, as pointed out above, neither interrupts gastro-intestinal motility nor profoundly modifies the gastro-intestinal movements. There is a strong tendency on the part of the system, furthermore, to restore normal functional activity in a relatively short time following the disturbances which arise as the result of such operative interference. For example, bilateral vagus section at the level of the diaphragm results in diminution of tonus of the gastro-intestinal musculature and retardation of peristalsis but both tonus and peristaltic activity are soon restored to the condition which existed before vagotomy. Bilateral section of the splanchnic nerves results in increased tonus and augmented peristaltic activity. This also subsides in a relatively short time and in some instances is followed by a hypotonic condition. Section of both vagus and splanchnic nerves results in marked hypotonicity of the stomach and retardation of peristalsis. This condition is of longer duration following bilateral than following unilateral section of these nerves (Bickel, 1925). Section of the sympathetic nerves supplying the large intestine not uncommonly results in mild diarrhea which gradually subsides. In our experimental animals (cats and dogs), frequent discharge of soft feces was observed in many instances for some time following removal of the inferior mesenteric ganglia or extirpation of the lumbar sympathetic trunks. Relief of chronic constipation in man also has been reported following lumbar sympathectomy.

The nervous phenomena involved in the normal functioning of the digestive tube obviously cannot be adequately explained on the basis of motor and inhibitory control mediated through the sympathetic and parasympathetic outflows from the central nervous system. Many reactions involve only the enteric nervous system. Gastro-intestinal motility of all known types has been observed following section of the extrinsic nerves supplying the part of the digestive tube in question. This motility, though normally subject to central nervous influences through the extrinsic nerves, originates in the neuromuscular mechanism in the wall of the

gastro-intestinal canal Gastro-intestinal motility of certain types probably is myogenic, but many of the reactions which commonly are recognized as reflexes are initiated in the enteric nervous system and carried out through it The reciprocal inhibition involved in the coördinated activity of the two muscle layers also requires the functioning of the enteric nervous mechanisms (Krishnan, 1933)

Enteric Conduction —Conduction within the wall of the digestive tube is a function of the enteric nervous system According to Alvarez (1929) the rate of travel of peristaltic rushes in the intestine of the rabbit is practically unaltered following section of the vagus nerves, the intestine is abnormally sensitive to faradic stimulation but the gradient of sensitivity from the duodenum distalward remains unchanged The rate of travel of peristaltic rushes also remains unaltered following section of the splanchnic nerves The latent periods in all parts of the intestine, except the duodenum, are shortened but the normal gradient of the latent periods remains unchanged In rabbits which survived three weeks or longer, following bilateral section of both vagus and splanchnic nerves peristaltic rushes still traveled at a normal rate but the latent periods were shortened as in rabbits subjected only to bilateral section of the splanchnic nerves

In another series of experiments on rabbits, Alvarez (1930) showed that conduction is stopped at a scar following section of all the layers of the intestine except the mucosa, but peristaltic rushes are not interrupted by such a scar because they push intestinal contents ahead, causing mechanical dilatation of the segment just distal to the scar The same phenomenon may be observed in an intestine which is cut through and the proximal and distal portions joined together by a glass tube Lawson and Templeton (1932) also reported that peristalsis, as a wave of contraction, does not pass from the proximal to the distal segment over a transection of the large intestine of the dog in the region of the splenic flexure

The conduction of wavelets produced by local electrical stimulation according to Alvarez (1930), is not changed following degeneration of the vagus nerves but is interfered with following degeneration of the splanchnic nerves In the small intestine of the rabbit, such waves of contraction normally travel 1 to 5 cm oralward and 1 to 20 cm aboralward In Alvarez s experiments, the modal distances were 5 cm oralward and 10 cm aboralward The mean rate of conduction varied from 5 cm per second in the duodenum to 3 8 cm per second in the lower ileum

The observation that stimulation of the intestine of the rabbit at any point gives rise to a wave of contraction which travels both oralward and aboralward from that point, repeatedly reported by Alvarez, is contrary to the observation of Bayliss and Starling (1899, 1900) that stimulation of the small intestine usually results in contraction above and relaxation below the point at which the stimulus is applied The so-called 'law of the intestine,' which is based on this observation of Bayliss and Starling according to the findings of Alvarez, does not obtain in the rabbit On the basis of a careful study of successive pictures of a cinema film taken of a rabbit's intestine, under a bath of salt solution during the progress of peristaltic rushes, Alvarez and Zimmerman (1927) concluded that "what looks occasionally like descending inhibition is really distention due to the advanced column of intestinal contents"

Enteric Reflexes — As observed by Cannon (1906), the differences in the rate of discharge of different kinds of food from the stomach persist following bilateral section of both splanchnic and vagus nerves. Relaxation of the pyloric sphincter when the contents of the pyloric antrum become acid also occurs in the excised stomach (Cannon 1907). According to Brunemeier and Carlson (1915), mechanical and chemical stimulation of the upper part of the intestinal mucosa inhibits gastric tonus and hunger contractions. These reactions persist but are less marked following bilateral section of both vagus and splanchnic nerves. It may be assumed, therefore, that these and similar responses elicited by stimulation of the gastric mucosa involve local as well as cerebrospinal reflex mechanisms. Mechanical irritation of the duodenal mucosa through a duodenal fistula in dogs with extrinsic nerves to the stomach and intestine intact, as observed by Luckhardt, Phillips and Carlson (1919), elicits tonic contraction of the pyloric sphincter. The same phenomenon was observed by Thomas and Kuntz (1926) in dogs which had been subjected to bilateral section of both vagus and splanchnic nerves. This reaction could not be elicited when conduction through the local neuromuscular mechanism was arrested by compression of the wall of the proximal portion of the duodenum between a ligature on the outside and a solid cylindrical body in the lumen. It obviously may be carried out as a reflex through the local neuromuscular mechanism at least in the absence of intact extrinsic nerves.

Exner (1902) observed that sharp metallic objects, *e g*, pins and needles introduced into the digestive tubes of experimental animals with their food, not infrequently pass through and are discharged in the feces without having penetrated the gastro-intestinal wall or injured the mucous epithelium. On examination of the intestine while pins and needles were passing through it, these objects commonly were found lying in longitudinal grooves in the mucosa, the majority of the pins being located with the head aboralward. According to Exner, the stomach and intestine possess in the muscularis mucosæ a mechanism which is adapted to protect the epithelium against injury by pointed foreign bodies. When a pointed body touches the epithelium it forms a groove, *i e*, the epithelium evades the pointed object and effects contact with the foreign body in a manner which is least likely to cause injury. In a study of the motility of the muscularis mucosæ and the intestinal villi, King and Arnold (1922) described retraction of the villi and ridging and pitting of the mucosa in response to mechanical and chemical stimuli applied to the intestinal epithelium. Since these phenomena also occurred following section and degeneration of the splanchnic nerves, they interpreted them as local reflexes mediated through the local neuromuscular mechanism.

After studying the motility of the large intestine following section of the extrinsic nerves, Bayliss and Starling (1900), Elliott and Barclay-Smith (1904), and Langley and Magnus (1905) all concluded that peristalsis in the large intestine also involves a local reflex mechanism. In animals in which the spinal cord had been destroyed, Lyman (1913) observed that antiperistalsis in the large intestine ceases when food material enters it from the ileum. This also involves reflex activity of the enteric nervous system. As pointed out above, the defecation reflex also may be restored following destruction of the spinal center through which it normally is carried out. In experiments reported by Raiford and Mulinos (1934),

involving localized stimulation of the mucosa in exteriorized pieces of the dog's colon, reflex muscular responses to mild mechanical stimulation persisted following section of the extrinsic nerves. In unanesthetized dogs localized stimulation of the colonic mucosa was followed by contraction of the longitudinal muscle at the site of the stimulation and distal to it and by contraction of the circular muscle, three to five seconds later, at the site of the stimulation and proximal to it.

The various gastro-intestinal reactions just referred to and certain others commonly are regarded as reflex activities. Inasmuch as all these reactions may be carried out following section of the nerves through which they might be mediated as cerebrospinal reflexes, it must be conceded that the enteric nervous system includes mechanisms through which coördinated reflexes are carried out.

Rhythmic Gastro-Intestinal Contractions.—Not a little experimental evidence has been advanced which seems to indicate that the purely rhythmic contractions of the gastro-intestinal musculature are myogenic. According to Bayliss and Starling (1899), the rhythmic contractions of the small intestine persist following the administration of drugs in doses which they regarded as sufficient to paralyze the myenteric plexus. They also observed, under these conditions, that waves of contraction which, unlike peristaltic contractions, are not preceded by inhibition, advance indifferently in either direction along the small intestine. According to Elliott and Barclay-Smith (1904), antiperistalsis in the large intestine persists following the administration of nicotine in doses sufficient to abolish peristalsis in the small intestine. According to Cannon (1909), gastric peristalsis persists following the administration of nicotine in large doses or multiple incisions through the muscular layers of the stomach which he regarded as sufficient to interrupt the continuity of the myenteric plexus. He also reported that the rhythmic contractions in the small intestine are not abolished by multiple incisions through the muscular layers (Cannon, 1912).

Bayliss and Starling (1899) advanced the theory that the rhythmic contractions of the intestine, i. e., those which persist after the coördinated movements which they regarded as reflex are abolished, are myogenic. This conclusion may be essentially correct, but it cannot be regarded as fully substantiated by the results of their experimental work with nicotine. The inference that the enteric plexuses are no longer functional following abolition of the myenteric reflex is untenable. As observed by King and Arnold (1922), responses of the intestinal villi to chemical and mechanical stimulation of the intestinal epithelium are not abolished by nicotine until it is present in sufficient concentration to paralyze the muscularis mucosæ. They interpreted these reactions as reflexes mediated through the submucous plexus. They seemed to be of the opinion that this plexus is not affected by nicotine in the same manner as, according to current conceptions, this drug affects other autonomic ganglia. They were not convinced that nicotine paralyzes the myenteric plexus. Thomas and Kuntz (1926) have shown that the influence of the vagus on the small intestine, as judged by the motor effects of vagus stimulation, is not abolished by doses of nicotine many times as large as the dosage which, in the experiments of Bayliss and Starling, abolished the peristaltic reflex. The dosage employed by Bayliss and Starling (2 to 3 cc. of a 1 per cent solution for a small dog), if not increased, holds the manifestation of the typical effects of vagus

stimulation in abeyance When nicotine is administered in greatly increased doses, vagus stimulation again becomes effective and remains so until the drug is present in a concentration representing 2 to 3 grams of the undiluted alkaloid per kilogram of body weight (Thomas and Kuntz 1926) This finding has been confirmed by Mulinos (1927) and Alvarez (1931) The small dosage of nicotine employed by Bayliss and Starling obviously does not paralyze the vago enteric mechanism but holds certain of its functions in abeyance probably by a process of inhibition The results of the experiments of Bayliss and Starling consequently do not demonstrate the myogenic nature of the rhythmic contractions which persist following abolition of the myenteric reflex by small doses of nicotine

The experimental results recorded by Magnus (1905) Gunn and Underhill (1914), and Alvarez and Mahoney (1922) are more convincing but not conclusive These investigators took advantage of the fact that the longitudinal muscle, with the major portion of the myenteric plexus adhering to it, and the submucosa, including the submucous plexus may be separated from the circular muscle They proceeded on the assumption that circular muscle isolated in this manner is practically free from nervous elements especially if only the deeper layers are retained All these investigators observed rhythmic contractions in strips of intestinal muscle isolated in this manner, although Magnus observed them only after the use of stimulating drugs These results were interpreted as indicating that intestinal muscle may contract rhythmically in the absence of nerve impulses at least under certain conditions This interpretation was criticized by Van Esveld (1928) on the basis of his observations on preparations of the intestine of the cat which revealed the existence of ganglion cells imbedded in the circular muscle layer In view of this finding it cannot be assumed that any portion of the circular muscle is completely denervated by mechanical separation Even though complete denervation could be assumed the results reported by the investigators named above would not prove that the rhythmic contractions of the gastro-intestinal musculature in the intact animal are independent of nervous control

Certain experimental data seem to indicate that even the rhythmic contractions of the gastro intestinal musculature in the presence of the intact enteric nervous system, are subject to nervous influences According to Roger (1906), the strength of the rhythmic segmenting contractions in the intestine is influenced by the nature of the intestinal content He observed that the segmenting contractions were weaker when the intestine was filled with a sodium chloride solution than when it was filled with a solution of sugar or peptone Yanase (1907) also reported that he could observe no spontaneous movements of the digestive tube in embryos of the guinea-pig until the myenteric plexus had developed

In an experimental study involving the use of nicotine in massive doses Thomas and Kuntz (1926) have shown that rhythmic gastric and intestinal contractions both in the intact animal and in excised pieces of the stomach and intestine persist following complete paralysis of the enteric nervous system but the kymographic records of these contractions differ characteristically from the records of rhythmic contractions obtained while the enteric nervous system remains functional In so far as the results of these experiments indicate that the gastro-intestinal musculature possesses the inherent capacity to contract rhythmically, they corroborate the find-

ings of those investigators who regard the rhythmic contractions of the stomach and intestine as myogenic but they neither indicate that these rhythmic contractions are normally carried out without nervous control nor that the gastro-intestinal musculature could adequately perform even its simpler motor functions in the absence of nervous regulation The rhythmic gastro-intestinal contractions which persist after the enteric nervous system is paralyzed differ widely from those carried out in the unpoisoned organs The records of even the simplest forms of rhythmic activity in an unpoisoned segment of the intestine, in which functional activity of the enteric nervous system may still be assumed, are characterized by frequent changes in tonus and amplitude which show a high degree of variation and complexity None of these irregularities appear in the records obtained following denervation with nicotine The movements which persist consist of mechanically regular contractions and relaxations While the records obtained before the administration of nicotine cannot be regarded as representing strictly normal functional activity, the difference between the extremely variable activity of the unpoisoned viscus and the mechanical regularity exhibited by the denervated preparation probably represents in some measure the functional control normally exercised by the enteric nervous system The frequent changes and irregularities observed in the records of the activity of the unpoisoned viscus under experimental conditions probably represent the functional activity of a nervous mechanism which is capable of bringing about similar changes in an orderly and purposeful sequence under the influence of the stimuli of its natural environment

As the dosage of nicotine was increased in both the experiments carried out on excised pieces of the intestine and those carried out with the stomach and intestine *in situ*, the amplitude of the rhythmic contractions increased progressively until the concentration of nicotine became relatively high and then gradually decreased Assuming that the influence of nicotine in moderate doses is exerted mainly on the neural mechanism, this fact suggests a functional relationship of the enteric nervous system to the amplitude of the rhythmic contractions Since all activity ceased in very high concentrations of nicotine, it seems highly probable that the gradual reduction in the amplitude of the rhythmic contractions, after the maximum amplitude was reached was due to the depressing effect of nicotine in high concentration on the muscle directly The cause of the progressive increase in amplitude which preceded this depression is less apparent It may be the primary stimulating effect of nicotine on the muscle preceding the depression On the other hand, the gastro intestinal musculature normally may be subject to inhibitory influences exerted by the enteric neural mechanism Such inhibitory influences would be removed as soon as the neural mechanism became materially depressed by nicotine The fact that preparations of excised intestine which, when first set up, are quiescent may be thrown into action promptly by the administration of sufficient nicotine to materially depress the neural mechanism, favors the latter possibility Both stimulation of the muscle and removal of nervous inhibition probably play a part in the phenomenon in question

The rate of the contractions is not increased in proportion to the increase in amplitude as the dosage of nicotine is increased Nerve stimulation furthermore, does not exert a constant effect on the rate of contraction

On the other hand, the depressing effect of nicotine in high concentration affects both the amplitude and the rate of the contractions. These facts suggest that the effect of removal of inhibition may be quantitatively greater than the effect of direct stimulation of the muscle in increasing the amplitude of contraction. They also suggest that the inhibition, which is generally regarded as responsible for the quiescence of the gastro-intestinal musculature, so commonly observed following operative procedures or manipulation of these organs, is not the result of reflexes involving the extrinsic nerves alone but, as Bayliss and Starling assumed, is due in part to inhibitory influences exerted through the enteric nervous system.

The relative constancy of the rate of the rhythmic contractions as compared with the great variability in tonus and amplitude under the influence of drug action and nerve stimulation by means of the galvanic current, throughout these experiments suggests that the rate may be quite independent of the nervous influences which bring about changes in tonus and amplitude. The rate of the rhythmic contractions probably depends on properties which are inherent in the gastro-intestinal musculature and, therefore, is subject to nervous control in a lesser degree than tonus and amplitude.

The results of these experiments seem to indicate quite clearly that the rhythmic gastro-intestinal contractions are myogenic in the sense that they may be initiated and carried out in the absence of nerve impulses but that they are normally subject to regulatory control which, at least in the absence of functional extrinsic nerves, must be mediated through enteric neural mechanisms.

Inasmuch as the effect of vagus stimulation is held in abeyance and certain of the gastro-intestinal movements are abolished by the effect of nicotine in moderate dosage, it has been assumed by some that any functional activity manifested by the enteric nervous system following the administration of moderate doses of nicotine must be mediated by asynaptic neural mechanisms. In the light of the experimental results here cited, this assumption is unnecessary. As we have seen, when the dosage of nicotine is progressively increased, vagus stimulation, the effect of which was held in abeyance by the smaller doses of nicotine, again becomes effective and remains so until nicotine is present in sufficient concentration to paralyze the enteric neural mechanism, consequently, there must be synapses in the vagus efferent chains which are as resistant to nicotine paralysis as the neuromuscular junctions themselves. If, as indicated by some of the anatomical data set forth above, some enteric neurons actually make synaptic connections with others, these synapses probably are equally resistant to nicotine paralysis. It seems highly probable, therefore, that whatever functional activity persists in the enteric nervous system following the administration of nicotine in moderate dosage is true reflex activity. This view obviates the necessity both of denying the regulatory nervous control of rhythmic gastro-intestinal contractions under physiologic conditions and of postulating the existence of synaptic nerve nets in the enteric nervous system.

In view of the fact that the coördinated reflex activities of the gastro-intestinal musculature may be carried out apparently according to their normal physiologic mode in the absence of central nervous influences, the enteric nervous system must be regarded as more complex both in its

anatomic structure and physiologic functions than other peripheral plexuses, e g, the cardiac and pulmonary plexuses It seems most reasonable to regard it as a reflex system capable of independent coordinated reflex activity but subject to reflex motor and inhibitory influences through the central nervous system

Nervous Regulation of Intestinal Secretion —Under normal conditions, the secretory activity of the intestinal glands depends in a large measure on the intestinal contents The glands in the small intestine normally secrete very little or not at all while the intestine is at rest Mechanical stimulation of the mucosa calls forth an immediate flow of secretion from these glands The quality of this secretion also depends on the character of the mechanical stimulus employed In Glinski's (1891) experiments, the introduction of a pledget of wool into the intestine through an artificial opening and its passage to another artificial opening farther distalward resulted in the production of a watery secretion containing very little mucus The introduction of dry peas through the same opening and their passage to the more distal one resulted in the production of a less watery secretion containing much more mucus In general glandular activity elicited by direct mechanical stimulation of the intestinal mucosa involves only a localized area of the intestine This fact strongly suggests that the reflex mechanisms employed involve only neurons in the enteric plexuses

Sawitsch and Soshestvensky (1917, 1921) demonstrated a secretory influence of the vagi on the intestinal glands in spinal animals (cats) In their experiments vagus stimulation resulted in an increase in both the liquid and enzyme contents of the intestinal secretion Within certain limits, the enzyme content of the intestinal secretion increased with increasing strength of stimulation regardless of the quality of liquid secreted Administration of atropine in moderate doses resulted in diminution of the secretory effect of vagus stimulation and, in large doses abolished it entirely Abolition of the secretory effect of vagus stimulation on the intestinal glands required larger doses of atropine than abolition of the vagus effect on intestinal motility This finding was regarded by Sawitsch and Soshestvensky as supporting the theory that secretory activity of the intestinal glands and intestinal motility are independent of each other

Section of the extrinsic nerves supplying a given portion of the intestine is followed by continuous secretory activity of the glands in that portion This has been called paralytic intestinal secretion Possibly the vasodilatation which follows section of the extrinsic nerves is a factor in the output of intestinal secretion under these conditions Molnar (1909) advanced experimental data which indicate quite clearly that the abundant and continuous secretory activity of the intestinal glands following section of the extrinsic nerves of the intestine is due mainly to the elimination of normal inhibitory nerve impulses These data like the data bearing on the effects of vagus stimulation, suggest that the secretory activity of the intestinal glands normally is subject to a measure of regulatory nervous control

In experiments reported by Wright *et al* (1940), vagus stimulation, in decerebrate and decapitate cats, elicited secretory activity of Brunner's glands in the duodenum but none in the jejunum or ileum Section of the greater splanchnic nerves in the thorax also resulted in secretory activity in the duodenum only but section of all the preganglionic sympathetic

nerves to the intestine resulted in secretory activity throughout the small intestine. The secretions from all parts of the intestine contained amylase, enterokinase, and traces of invertase and lipase but no protease or peptidase.

Schiffrin and Nasset (1939) reported diminution of enzyme concentration and total enzyme secretion in jejunal and ileal segments of the dog's intestine following feeding, lasting from six to eight hours. This effect was reversed following section of the extrinsic nerves.

Intestinal secretion is regulated in part by the intestinal contents and substances circulating in the blood. Molnar (1909) found that the intravenous injection of meat extractives in dogs results in increased intestinal secretion. In man, according to Bickel and Wagner (1934), albuminous and fatty foods call forth greater secretory activity in the small intestine than carbohydrates. Powdered pancreatic substance also strongly stimulates the intestinal glands. The secretory activity of the glands of the small intestine in man is not continuous but intermittent, even in the presence of stimulating food material. In the intact animal the intestinal glands also secrete intermittently even though the stimulating substances in the blood are increased by artificial means. Molnar's experimental results led him to conclude that the intestinal gland cells are continuously influenced directly by hormones circulating in the blood but their secretory activity is normally held in check by inhibitory nerve impulses. Brestkin and Sawitsch (1927) also supported the theory that the nervous regulation of the secretory activity of the intestinal glands consists mainly in inhibition. This also is in full accord with the discovery of Volborth (1925) that secretin is a normal constituent of the intestinal juice.

CHAPTER XI

INNERVATION OF THE BILIARY SYSTEM

Extrinsic Nerves.—The innervation of the biliary system is derived mainly from the celiac plexus and the vagi. The phrenic plexus probably contributes to the biliary nerves in some instances. The nerves which supply the liver, gall bladder and bile ducts form a plexiform structure which may be subdivided into an anterior and a posterior hepatic plexus (Raigorodsky, 1928). The anterior hepatic plexus is located in relation to the hepatic artery, around which it forms a dense meshwork. It is derived mainly from the left portion of the celiac plexus and the right abdominal branch of the left vagus which approaches the hepatic portal via the hepatogastric ligament. Some of its branches join the celiac plexus. The anterior hepatic plexus includes the internal nerve to the cystic duct and the gall bladder and the nervus pancreaticocholedochus. The posterior hepatic plexus is located in relation to the portal vein and the bile duct. It is derived mainly from the right portion of the celiac plexus and branches of the right vagus which traverse this plexus. It includes three or four main trunks which take a transverse course behind the portal vein and reach the posterior surfaces of the bile ducts. The right lateral trunk assumes a position along the posterior surface of the common bile duct and is distributed mainly to this duct. It gives rise to the lateral nerve of the gall bladder and some anastomotic rami to the anterior hepatic plexus.

The major ganglion in the right portion of the celiac plexus usually is larger than the one in the left portion and probably contributes the major portion of the sympathetic fibers in the biliary nerves (Alexander, 1940). Rami arising from both the right and left portions of the celiac plexus contribute to the plexiform structure on the hepatic artery and mingle to some extent in the anterior and posterior hepatic plexuses. The plexiform structure in the hepatic portal includes numerous small ganglia.

In those cases in which the phrenic nerve contributes to the innervation of the liver, according to Raigorodsky (1928), phrenic branches join sympathetic rami which enter the liver either through the hepatic portal or near the posterior hepatic border. In some instances branches of the phrenic nerve join hepatic rami of the left vagus.

The innervation of the choledochoduodenal junction appears to be particularly abundant. In the cat, according to Schulze and Boyden (1943), this region is supplied through two independent pathways, the gastroduodenal nerve and the gastroduodenal plexus. The gastroduodenal nerve arises by confluence of branches of the hepatic plexus which include fibers derived from both right and left celiac ganglia, and branches of the celiac division of the right vagus (Fig. 60). One of its two main branches terminates at the junction of the bile duct and the intestine. The gastroduodenal plexus, associated with the gastroduodenal artery, is made up of fibers derived from the hepatic plexus and a few recurrent fibers of the coronary nerve. Both pathways contribute fibers to the paracholedochal plexus. At the choledochoduodenal junction those derived from the gastroduodenal plexus tend to follow the superior pancreaticoduodenal artery and

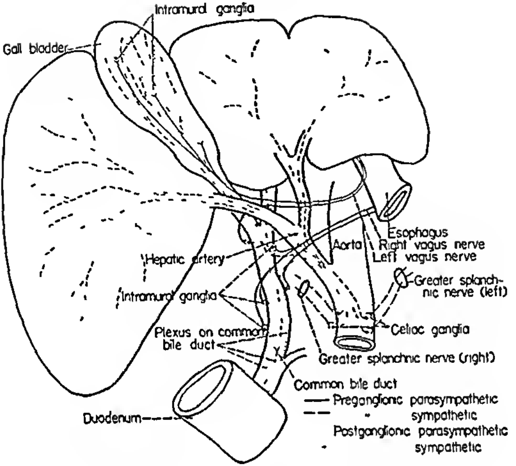


FIG 59 —Diagrammatic illustration of the innervation of the biliary system

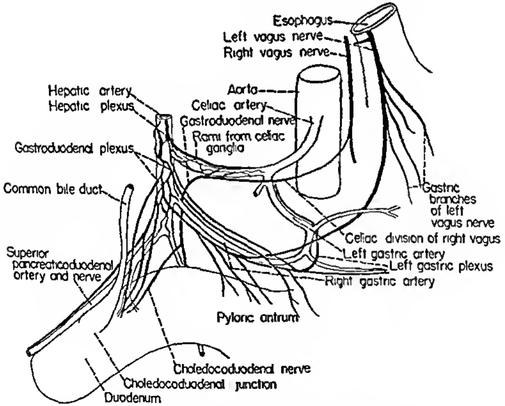


FIG 60 —Diagrammatic illustration of the extrinsic innervation of the choledochoduodenal junction in the cat (Redrawn from Schulze and Boyden 1943)

its branch, the common duodenal artery. Those derived from the gastroduodenal nerve terminate both in the intrinsic plexus of the bile duct and adjacent portions of the myenteric plexus.

Intrinsic Nerves.—As the hepatic artery and portal vein enter the liver, they are accompanied by nerves made up mainly of unmyelinated fibers. These nerves give rise to branches which continue along the branches of the blood vessels and bile ducts. In Golgi preparations, Berkeley (1893) described the nerves associated with the hepatic vessels and bile ducts as delicate plexuses and pointed out that the supply to the hepatic artery is more abundant than that to the portal vein. Various investigators, particularly Berkeley (1893), Wolf (1902), Greving (1921) and Reigele (1928), have supported the assumption that nerve fibers penetrate the liver lobules and terminate in relation to liver cells. The results of most of the more recent investigations do not support this point of view.

The intrahepatic nerves, as observed by Alexander (1940), comprise mainly unmyelinated fibers and a limited number of myelinated ones. The latter probably are visceral afferents. In general these nerves are closely associated with the blood vessels and bile ducts to which they are functionally related. Alexander could trace no nerve fibers into the parenchyma of the liver lobules.

The intramural nerves of the bile ducts and the gall bladder form irregular plexuses in the adventitia, the muscularis and the submucosa. The adventitial and intramuscular plexuses include small ganglia at their nodal points (Dogiel, 1899, Harting, 1931). These plexuses are intimately connected with one another and with the submucous plexus which probably includes no ganglia. Alexander (1940) reported individual ganglion cells in this plexus in the gall bladder. Fibers of the submucous plexus approach the epithelium but probably do not penetrate into it.

At the choledochoduodenal junction, according to Schulze and Boyden (1943), the more delicate choledochal plexus and the heavier myenteric plexus are connected by strands of nerve fibers, but there is no direct continuity of the one plexus with the other. In the sphincter of Oddi, as demonstrated by Boyden and Van Buskirk (1943) in the cat, the intrinsic plexus includes numerous small ganglia. This plexus undergoes no marked change due to degeneration of the fibers of extrinsic origin.

In experiments reported by Alexander (1940), bilateral degeneration of the vagus nerves did not appreciably alter the abundance and distribution of nerve fibers in preparations of the biliary system, except in the hepatic portal where the myelinated fibers were reduced in numbers in some of the nerves accompanying the blood vessels and bile ducts. Extirpation of the celiac ganglia cannot be carried out without also interrupting part of the vagus supply to the biliary system. This operation resulted in almost complete degeneration of the intrahepatic nerves, except for some fibers in the nerves associated with the bile ducts. It probably completely eliminated the vascular innervation and materially reduced the numbers of intramural fibers in the bile ducts and the gall bladder. Bilateral vagus section and extirpation of the celiac ganglia resulted in degeneration of nearly all the fibers in the extrinsic biliary nerves, complete degeneration of the nerve supply to the blood vessels throughout the biliary system and degeneration of all the fibers in the walls of the bile ducts and the gall bladder except those arising in the intramural ganglia and ganglia in the

hepatic portal. These results support the assumptions that the efferent innervation of the hepatic blood vessels is solely sympathetic and that the musculature of the bile ducts and the gall bladder is innervated through both sympathetic and parasympathetic nerves.

Nervous Regulation of Liver Functions.—Intrahepatic Vasomotor Regulation.—Functional sympathetic innervation of the intrahepatic vessels has been amply demonstrated but the data bearing on the possible influence of parasympathetic nerves on these vessels are not in complete agreement. Stimulation of the splanchnic nerves or the hepatic plexus uniformly elicits constriction of the hepatic arterioles and the terminal branches of the hepatic portal vein, causing a rise in portal pressure (Bayliss and Starling, 1894, Cavazzani and Manca, 1895). The inflow of blood, consequently, is reduced. The same stimulus results in an increased outflow from the liver, consequently, liver volume is reduced (Thompson, 1899, Burton-Opitz, 1914, Griffith and Emery, 1931, Bauer *et al.*, 1932, Eckhardt, 1935). Thus, the liver, like the spleen, under certain conditions plays a role in the regulation of the systemic blood pressure. (See Chapter VIII.) Changes in intrahepatic circulation also play a role in the metabolic and secretory functions of the liver.

Certain investigators (Neubauer, 1913, Carnot *et al.*, 1930) have reported effects of vagus stimulation on intrahepatic circulation. Others, on the contrary, have failed to demonstrate an appreciable effect of parasympathetic stimulation on the flow of blood through the liver (Bauer *et al.*, 1932, McMichael, 1937, Wakim, 1942). In Wakim's (1942) experiments, carried out on amphibia and small mammals with the aid of transillumination of the liver, stimulation of the hepatic plexus caused constriction of the intrahepatic vessels, including the sinusoids, whereas vagus stimulation produced no perceptible effect on the intrahepatic vessels.

Bile Secretion.—The earlier physiologists, including Heidenhain (1883), found no evidence of nervous influences in the secretion of bile. Certain investigators have reported both qualitative and quantitative changes in the bile output due to nerve stimulation (Eiger, 1916) and nerve section (Gaissinsky, 1928).

The secretion of bile continues uninterruptedly, but the rate of secretion varies from hour to hour and under varying conditions of nutrition. During periods of fasting it is very low and is increased but little after a meal of carbohydrates but considerably after a meal of fat and still more markedly after a meal of proteins. In experiments reported by Hillyard (1930, 1931) and Lindberg (1931) corresponding changes in the output of bile after meals of carbohydrate, fat and protein respectively were observed in dogs following complete denervation of the liver.

Although the secretion of bile is not directly influenced by nerve impulses, it is definitely altered by changes in intrahepatic blood pressure. In experiments reported by Tanturi and Ivy (1938) acute increases in hepatic portal venous and hepatic arterial pressure resulted in diminished bile output. Occlusion of the hepatic artery resulted in augmentation of the bile output for at least a few hours. Stimulation of the sympathetic nerves to the liver results in diminished bile production due to its vasoconstricting effect. In general, reduction in the blood volume flow through the liver results in a decrease in the output of bile, whereas an increase in the blood flow results in an increase in the bile output except when the

increase in the blood flow is associated with increased intrahepatic blood pressure

In one series of experiments Tanturi and Ivy (1938) obtained data which seemed to indicate a direct effect of vagus impulses on the production of bile in the dog and the monkey but not in the cat or the rabbit. They reported an excitatory-secretory effect in the dog and the monkey produced by stimulating the peripheral end of the vagus in the neck five days after section of this nerve. They also reported augmentation of bile secretion in the dog elicited by stimulating the central end of the divided vagus while the other vagus remained intact. Section of the second vagus abolished this effect. When both vagi were divided stimulation of the central end of one of them resulted in diminished bile secretion. These results seem to indicate both direct and reflex effects of vagus stimulation on bile secretion. In view of the functional capacity of the liver following section of all its extrinsic nerves and the absence of conclusive evidence of nerve fibers within the liver lobules they probably can be explained without the necessity of postulating direct contact of nerve fibers with the liver cells.

Carbohydrate Metabolism.—Stimulation of the center for carbohydrate metabolism in the floor of the fourth ventricle not uncommonly results in hyperglycemia and glycosuria. Claude Bernard (1887) observed that puncture of this center is not followed by glycosuria or hyperglycemia in animals whose supply of glycogen has been depleted by continued fasting. He also observed that section of the spinal cord in the lower thoracic region does not prevent glycosuria following stimulation by puncture of the so-called sugar center, but that such stimulation has no influence on the conversion of glycogen into sugar following section of the spinal cord in the upper thoracic region. This lead him to conclude that puncture of the medullary center in question stimulates sugar production only in the liver and that the efferent impulses which bring about this result reach the liver through the splanchnic nerves. The results of more recent experiments indicate that these impulses are conducted from the spinal cord via the fifth and sixth thoracic nerve roots. That the liver is the seat of the increased sugar production following puncture of the sugar center is also indicated by the fact that glycosuria does not follow this operation when the hepatic vessels are ligated.

The carbohydrate center probably receives a constant influx of afferent impulses, particularly through the vagi, which play an important role in the regulation of the normal production of sugar in the liver. Pflüger (1903) advanced the theory that the body, by virtue of this reflex mechanism, is enabled to draw upon the food supply represented by the glycogen in the liver whenever an increased expenditure of energy is required. For example, when a particular group of muscles, through prolonged activity, has exhausted its local food supply, afferent impulses are conveyed to the medulla which activate the carbohydrate center and thus bring about the release of energy-producing food material for immediate use.

Certain diencephalic centers, as indicated both by morphological and physiological data, also play a part in the regulatory control of carbohydrate metabolism. Brooks (1931) has demonstrated that reflex rises in blood sugar equal to those produced in animals with intact central nervous systems may be obtained after section of the brain stem below the mid

brain The higher centers, therefore, obviously are not necessary for the mobilization of carbohydrates as manifested in reflex rises in blood sugar

The data bearing on the influence of nerve impulses on carbohydrate metabolism are not unequivocal Claude Bernard (1887) advanced the theory, on the basis of his findings, that impulses emanating from the carbohydrate center effect circulatory changes in the liver which in turn influence liver functions Little was then known regarding the role of hormonal substances, such as adrenin and insulin, in carbohydrate metabolism Some of the later investigators, particularly Pfluger (1903), Starkenstein (1912) Eiger (1915) and Snyder (1937), have interpreted their experimental findings as supporting the assumption that nerve impulses influence carbohydrate metabolism by exerting a direct effect on the liver cells Others, *e g*, Asher and Correl (1918), have supported the theory that carbohydrate metabolism is regulated in part through the direct effect of nerve impulses on the liver cells and in part through hormonal substances Still others support the assumption that the influence of nerve impulses on carbohydrate metabolism is exerted mainly through their effects on the secretory activity of the appropriate endocrine glands The output of adrenin is known to be increased by sympathetic stimulation, the output of insulin by parasympathetic stimulation Stimulation of the carbohydrate center commonly results in an increased output of adrenin (Carrasco-Formiguesa, 1922) which in turn causes a rise in blood sugar Variations in the concentration of sugar in the blood according to Toenniessen (1924), constitute the chief physiologic stimuli for the carbohydrate center Injury to this center results only in temporary glycosuria Frank diabetes mellitus probably results only from disease of a peripheral organ involved in carbohydrate metabolism, particularly the pancreas Experimental data reported by Clark (1928) seem to indicate that the production of hyperglycemia by the intravenous injection of pituitrin is not influenced by autonomic nerve impulses Hill and Maycock (1939) reported no significant changes in the blood sugar level in cats due to cervical sympathetic stimulation in both acute and chronic experiments

In an experimental study on rabbits involving the administration of adrenin and insulin, Dresel and Omonsky (1927) observed lowered adrenin hyperglycemia and increased insulin hypoglycemia following bilateral vagus section and bilateral section of both the vagus and splanchnic nerves Donald (1931) reported the results of studies extending over a period of four months after section of the hepatic nerves, which indicate no modification in the fasting blood sugar, the hyperglycemia produced by adrenin, glucose and pituitary extracts, or the hypoglycemia produced by insulin due to denervation of the liver Edwards, Brouha and Johnson (1938) observed no difference in the increase in blood lactate due to exercise in normal and chronically sympathectomized dogs and no change in the blood lactate after injection of insulin or ingestion of glucose in either normal or sympathectomized dogs, but a greater increase following the injection of a given dose of adrenin in adrenalectomized or totally sympathectomized dogs than in normal ones Brouha, Cannon and Dill (1939) reported the results of experiments in which dogs, following total sympathectomy, with or without removal of the adrenal medulla, maintained a blood sugar balance within the normal range during exercise and following it after ingestion of glucose and after injection of adrenin, after adequate time

had been allowed for recovery from the operation The sympathectomized dogs remained sensitive to insulin for an indefinite period, due merely to denervation of the adrenals, since dogs deprived only of the adrenal medulla are no less sensitive to insulin than totally sympathectomized dogs In view of these findings, it may be assumed that the functions of the liver in carbohydrate metabolism are independent of direct effects of nerve impulses on the liver cells

Hypoglycemia is commonly accompanied by alterations in blood pressure, accelerated pulse rate, perspiration, etc, due to sympathetic stimulation and increased gastric motility and secretion due to parasympathetic stimulation These symptoms may be attributed to diencephalic stimulation They subside following the administration of sugar, since restoration of the blood sugar level removes the cause of the central stimulation (Fortuyn, 1941)

Protein Metabolism —Data which seem to indicate that protein metabolism in the liver is influenced by nerve impulses are not wanting According to Freund and Grafe (1912), this function of the liver is augmented by sympathetic stimulation and inhibited by parasympathetic stimulation On the other hand, the inherent capacity of the liver cells to break up proteins is not impaired by complete denervation of the liver The influence of nerve impulses in protein metabolism in the liver probably is exerted mainly through circulatory regulation

Nervous Regulation of Gall Bladder and Bile Ducts —The bile ducts and the gall bladder are provided with a muscular tunic and the opening of the common duct into the duodenum is guarded by a sphincteric mechanism the so-called sphincter of Oddi Excepting the smaller intrahepatic bile ducts, this system is innervated through both visceral afferent and autonomic nerves Afferent nerve fibers reach the biliary tract via both the splanchnic and vagus nerves Distention of the gall bladder and bile ducts according to Schrager and Ivy (1928), elicits pain which is abolished by section of the splanchnic nerves particularly the right, nausea and vomiting which are abolished by vagus section and respiratory disturbances which are diminished by section of either the splanchnics or vagi These findings have been corroborated by experimental data reported by Davis, Heart and Crum (1929) and by the use of spinal anesthesia in operations involving the gall bladder and bile ducts in man In a clinical study reported by Bergh and Layne (1940) the intense pain caused by suddenly distending the common bile duct could be correlated only with spasm of the sphincter of Oddi

On the basis of a review of the older literature bearing on the efferent innervation of the gall bladder, Mann (1924) concluded that both the vagi and the splanchnic nerves convey both motor and inhibitory fibers to this viscus but the vagi are predominantly motor and the splanchnics predominantly inhibitory The results of more recent studies, particularly those of Whitaker (1926), Burget (1927) and Crandall (1931), indicate no marked effect of vagus stimulation on the gall bladder in cats and dogs Since these results were obtained mainly in experimental attempts to ascertain whether evacuation of the gall bladder can be induced by vagus stimulation they should not be interpreted as indicating that the vagi exert no influence in the functional regulation of the gall bladder In

Westphal's (1923) experiments on guinea-pigs, vagus stimulation elicited contraction of the gall bladder and relaxation of the sphincter, resulting in the discharge of bile into the duodenum whereas splanchnic stimulation inhibited the rhythmic contractions of the gall bladder and peristalsis of the bile ducts and caused contraction of the sphincter Burget and Brochleburst (1927) obtained no evidence of contractions of the gall bladder in the guinea pig due to vagus stimulation Certain experimental data advanced by Burget (1925, 1926), Graham (1926) and Ivy (1937) support the assumption that the resistance to the flow of bile into the intestine is due to the tonicity of the duodenum rather than contraction of the sphincter of Oddi Higgins and Mann (1926) and Whitaker (1926) reported experimental data which seem to indicate that contraction of the sphincter may be a factor in the filling of the gall bladder

The reciprocal innervation of the gall bladder and the sphincter of Oddi has long been recognized Heidenhain (1863) attributed the first discharge of bile into the intestine after a meal to acid chyme in contact with the papilla of Vater which elicits reflex contraction of the gall bladder Foster (1880) regarded it as a reflex response involving contraction of the gall bladder and bile ducts accompanied by relaxation of the sphincter According to Rost (1913), the sphincter relaxes with every contraction of the gall bladder In discussing the reciprocal innervation of the gall bladder and the sphincter of Oddi in relation to gall bladder diseases, Meltzer (1917) pointed out that during storage of bile, the gall bladder is relaxed and the sphincter contracted, and that during discharge the gall bladder contracts and the sphincter relaxes He recommended the administration of a 25 per cent solution of magnesium sulphate by duodenal tube in certain cases of jaundice and biliary colic to relax the duodenal musculature and the sphincter of Oddi which would permit the escape of bile into the intestine

Kalk and Schondube (1926) described the response of the gall bladder in the dog to hypophyseal extract as a tonic contraction which involves mainly the corpus and fundus, causing the flow of bile to begin suddenly and continue rapidly until the gall bladder is empty Copher and Kodama (1926) observed a rise in pressure in the gall bladder with relaxation of the sphincter on injection of adrenin Using a method called "triple intubation" (cystic duct, proximal and distal ends of common duct cannulated with tubes leading to exterior) McMaster and Elman (1926), observed that the gall bladder pressure rose markedly and the sphincter resistance decreased on feeding or frequently on showing the animal food This work has been corroborated and extended by Kadokura and Katsuya (1930) by the use of a method involving a duodenal fistula They found that the bile did not flow into the intestine at once on feeding but in intermittent portions as the chyme entered the duodenum, thus pointing out the intermittent character of the relaxation of the sphincter The relaxation of the sphincter which accompanies contraction of the gall bladder is incomplete, according to Ivy (1937), and hypertonicity of the sphincter may result in biliary stasis In some cases spasm of the sphincter may be produced by distention of the bile ducts (Layne and Bergh, 1939) The tension developed in the gall bladder by stimulation such as that caused by a single submaximal dose of cholecystokinin depends on the initial pressure (Doubilet and Ivy, 1938)

Lueth (1931) confirmed the claim of Oddi (1894) that the sphincter has an independent nervous control, but pointed out that, although it may act independently, it is functionally coordinated with the mechanisms involved in duodenal peristalsis and tonus. Bergh and Layne (1940) demonstrated changes in the tonicity of the sphincter of Oddi in human subjects which seemed to be entirely independent of changes in the activity or tonicity of the duodenal musculature. In experiments on dogs reported by Necheles and Kozoll (1942), contraction of the sphincter of Oddi, in many instances was accompanied by contractions of the duodenum but the latter frequently did not affect the patency of the sphincter to a perfusion liquid, *i. e.*, sphincter and duodenal tonus frequently were independent of one another. Independent activity of the sphincter of Oddi and the duodenum also was observed, in their experiments, during contractions of the duodenum produced by various drugs. In human subjects sphincter resistance was increased by coughing, nausea and the passage of stools.

In a series of experiments reported by Birch and Boyden (1930), faradic stimulation of the pyloric portion of the stomach elicited contraction of the relaxed gall bladder. Faradic stimulation of the stomach, pylorus, small intestine or cecum, while the gall bladder was emptying after a meal of egg yolk, temporarily inhibited the discharge of bile. They also observed rhythmic contractions of the gall bladder which took place synchronously with the hunger contractions of the stomach. Such contractions of the gall bladder coordinated with the hunger contractions of the stomach probably account for the periodic emptying of the gall bladder during fasting. The results of these experiments demonstrate the existence of reflex pathways between the gastro-intestinal tract and the gall bladder. They also support the theory that dysfunction of the gall bladder or biliary stasis, at least in some instances, may be due to inhibitory reflexes from chronically diseased portions of the digestive tube. Du Bois and Kistler (1933) reported marked contractions of the gall bladder in response to faradic stimulation of the viscus itself, the duodenal portion (ampulla) of the common bile duct and either vagus nerve in its cervical portion. When the common bile duct was severed, stimulation of its duodenal portion no longer elicited contraction of the gall bladder but contraction of the latter organ was elicited by stimulation of the hepatic end of the severed bile duct. Their results were interpreted as evidence of the existence of a direct reflex pathway from the ampulla to the gall bladder along the wall of the bile duct but not as indicating that all reflex responses of the gall bladder to stimulation at the duodenal end of the bile duct are mediated through this pathway. Responses of the gall bladder to stimulation in this area, like those to stimulation in other parts of the gastro-intestinal tract, may be mediated through less direct reflex mechanisms.

In an experimental study on cats, reported by Johnson and Boyden (1943), interruption of the nerve fibers which reach the choledochoduodenal junction via the gastroduodenal plexus did not alter the rate of emptying of the bile passages following ingestion of food or abolish the inhibitory reflex from the cecum to the gall bladder. The efferent fibers in this plexus presumably are mainly vasomotor. Interruption of the gastroduodenal nerve resulted in marked retardation of the bile flow. Section of the right vagus resulted in even greater retardation of flow. This observation sup-

ports the assumption that the right vagus not only sends inhibitory fibers to the sphincter of Oddi via the gastroduodenal nerve but also motor fibers to the gall bladder via the hepatic plexus Interruption of the left vagus, which plays no part in the innervation of the sphincter of Oddi, resulted in retardation of emptying of the gall bladder but in a lesser degree Section of the splanchnic roots of the celiac ganglia abolished the inhibitory reflex from the cecum to the gall bladder and resulted in acceleration of emptying of the gall bladder in some degree

On the basis of their experimental results Johnson and Boyden advanced the opinion that the gastroduodenal nerve conveys no sympathetic fibers involved in maintaining the tonus of the sphincter of Oddi and suggested that the biliary outlet may be kept closed during fasting by the activity of the intrinsic neural mechanisms and that after meals the tonic contraction of the sphincter may be overcome by the inhibitory influence of the right vagus and by hormones produced in the intestinal mucosa They also pointed out that the reciprocal relationship between gall bladder and sphincter is not obligatory, since each responds to appropriate stimulation when the nerve to the other is interrupted

Influences emanating from the central nervous system under certain conditions, profoundly affect the biliary system Strong emotional disturbances, *e g*, rage or fright, may give rise to temporary icterus, probably due in part to biliary stasis caused by closure of the common bile duct either by increased tonicity of the duodenum or contraction of the sphincter of Oddi or both Under these conditions bile is absorbed into the blood with resulting icterus The peripheral pathways involved in this reaction are mainly vagus Emotional icterus, therefore falls within the realm of vagotonia Conversely, disturbances of the biliary system especially gall bladder disease, may give rise to afferent impulses which result in reflex vomiting, tachycardia, regional pruritus, perspiration dyspnea, salivation or inhibition of salivary secretion and pupillary disturbances (Thies, 1917) Such disturbances also result in changes in the content of cholin and cholin-like substances in the blood which profoundly affect the functional balance of the autonomic nervous system (Danielopolu 1930)

The data cited above support the assumptions that the biliary tract is subject to direct and reflex regulation through its nerve supply and that evacuation of the gall bladder is accomplished, under physiological conditions, by contraction of its intrinsic musculature Data which apparently do not support these assumptions are not wanting (Auster and Crohn, 1922, Wilkenstein and Aschner, 1925, Burget, 1927) but their consideration in this connection could serve no useful purpose The assumption that the fatty constituents of the food play a major role in the reflex regulation of the flow of bile from the gall bladder also is amply supported by both experimental and clinical data

Boyden (1925) reported experiments in which cats fed a diet of egg yolk and heavy cream immediately exhibited a functional periodicity of the gall bladder in relation to meals, and cats fed a pure protein and carbohydrate diet showed no marked volume changes in the gall bladder Boyden also demonstrated the effectiveness of fatty food, particularly egg yolk and cream in evacuating the gall bladder in man One hour and forty minutes after the beginning of a meal consisting of the yolks of four eggs and a pint

of cream, cholecystograms showed that the gall bladder had undergone a reduction in volume from the fully distended condition, due to going without food for eighteen hours, to a condition in which it was nearly empty. One hour later evacuation was apparently complete. By means of roentgen ray examination of patients, Boyden (1928) found that the time required for complete evacuation of the gall bladder after the ingestion of egg yolk or cream varies from sixteen minutes to four and one-half hours. The first phase of the contraction usually discharged three-quarters of the contents within thirty two minutes after the meal. In patients who had undergone surgical removal of the gall bladder, as reported by Bergh (1942), a meal consisting of egg yolk and cream produced relaxation of the sphincter of Oddi but fresh olive oil produced no appreciable effect. Relaxation of the sphincter was observed occasionally following a protein meal. Carbohydrate meals produced no significant effects on the sphincter resistance.

In a series of experiments carried out by Boyden and Birch (1930), the yolk of one egg injected into the duodenum in man elicited a single phase of contraction of the gall bladder which evacuated three-quarters of its contents. Bile could be aspirated from the duodenum seven to fifteen minutes after the injection of the yolk. Injection of a strong solution of $MgSO_4$, $MgCl_2$ or Na_2SO_4 elicited evacuation of two-thirds of the contents of the gall bladder and the bile could be aspirated from the duodenum in the same time as following the injection of egg yolk. When given by mouth, these salts are nearly as effective as when injected into the duodenum through a Rehfuss tube. Solutions of NaCl, Na_2CO_3 or Na_3PO_4 introduced into the duodenum elicit temporary relaxation and filling of the gall bladder. Alternating changes in the hydrogen ion concentration of the duodenal content seem to have no appreciable effect on the tonus of the gall bladder. Injection of liquid petrolatum into the duodenum causes initial inhibition of the gall bladder and retards its response to food injected subsequently. The latter effect probably is due to the local action of the petrolatum in closing the sphincter.

In man, as observed by Boyden, Bergh and Layne (1943), the gall bladder and the sphincter of Oddi react to egg yolk and to $MgSO_4$ introduced into the duodenum in the same manner and for the same length of time but not in the same degree. Egg yolk is more effective than $MgSO_4$, probably due to its more rapid rate of absorption and stronger chemical action. They have suggested that both these substances stimulate the production of hormones which act directly on both the gall bladder and the sphincter of Oddi and that these end organs react differently to a given stimulus. The initial response to either egg yolk or $MgSO_4$ usually is contraction of the sphincter, which in turn may interrupt the contraction of gall bladder which was initiated somewhat later, thus producing a pause. After four or five minutes, a phase of progressive relaxation of the sphincter is initiated which continues for an average period of seventeen minutes. During this interval, the main contraction phase of the gall bladder is initiated which continues for an average period of thirty minutes. On the basis of evidence obtained in animal experiments, they have advanced the opinion that the hormone acts upon the sphincter for a shorter time than upon the gall bladder because during fasting the tonus of the sphincter is maintained by

the local neural mechanism the threshold of stimulation of which is higher than that of the gall bladder

In a study of 115 individuals ranging from six to seventy-eight years of age, Boyden and Grantham (1936) found that gall bladder evacuation occurs more rapidly in children than in young adults Before puberty it occurs more rapidly in males than in females, after puberty more rapidly in females than in males If the biliary tract escapes pathologic alterations the rate of evacuation of the gall bladder is not retarded in advanced age It is slightly increased in patients with carcinoma of the stomach (Ritchie and Boyden, 1937) and markedly increased in patients with peptic ulcer (Boyden and Berman, 1937)

CHAPTER XII

INNERVATION OF THE PANCREAS, SPLEEN, THYROID, ADRENALS AND BONE MARROW

The Pancreas.—Extrinsic Nerves.—The innervation of the pancreas is derived from the celiac plexus mainly through the hepatic, superior mesenteric and splenic plexuses. Rami arising from the latter plexuses form plexuses on the pancreatic vessels. Thus the nerves enter the gland mainly along its blood vessels (Fig. 61). Isolated rami arising from the celiac plexus enter the pancreas directly without traversing the plexuses on the pancreatic vessels.

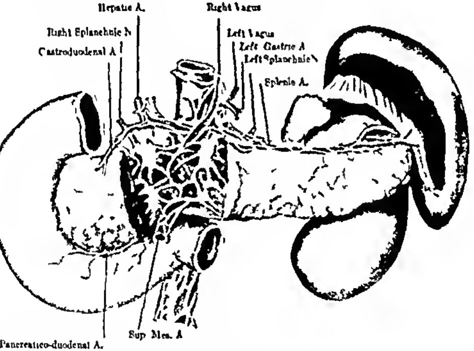


FIG. 61.—Diagrammatic illustration of the innervation of the pancreas and the spleen. (Modified from Greving.)

The pancreatic nerves include both sympathetic and parasympathetic components. Since both the splanchnic and vagus components involved traverse the celiac plexus, anatomic separation of the sympathetic and parasympathetic fibers is impossible. Certain experimental data reported by Babkin *et al.* (1939) support the assumption that the splanchnic secretory fibers, like the preganglionic vagus components, traverse the celiac plexus without effecting synaptic relays in its ganglia. The results of physiologic experimentation indicate that the sympathetic and parasympathetic fibers which enter the pancreas are functionally distinct.

Intrinsic Nerves.—Certain early investigators, notably Cajal (1891) and E. Muller (1892), described elements in the parenchyma of the pancreas which they regarded as ganglion cells. Certain others, particularly Gentes

(1902) and Pensa (1905), failed to corroborate these findings More recently the occurrence of ganglion cells in the pancreas in man and certain other mammals has been reported particularly by Ssobolew (1912), Van Campenhout (1925, 1927) and Simard (1937, 1942)

The nerve fibers within the pancreas are mainly unmyelinated As the nerves enter the gland, they continue for some distance along the arteries around which they form plexuses At intervals nerve fibers deviate from the blood vessels and give rise to periacinar plexuses Delicate fibers arising from the latter penetrate the membrana propria and terminate in slight bulb like enlargements between the basal portions of the gland cells (Cajal, E Muller) Similar plexuses also occur around the pancreatic islets Fibers arising from these plexuses penetrate the islets and ramify among the islet cells, forming a plexiform meshwork and finally terminating in free endings between the cells Both Gentes and Pensa emphasized the abundance of the nerve supply to the pancreatic islets as compared with the supply to the other parts of the gland

The site of origin of the postganglionic fibers is not definitely known The sympathetic vasomotor fibers undoubtedly arise in the celiac ganglia If as maintained by Babkin *et al* (1939) the secretory components of the splanchnic nerves traverse the celiac plexus without effecting synaptic connections in its ganglia, the postganglionic neurons synaptically related to these fibers must be located in the plexuses along the pancreatic vessels or within the pancreas Brugsch Dresel and Lewy (1921) mainly on the basis of Cajal s anatomical studies, assumed that the preganglionic vagus fibers actually enter the pancreas and effect synaptic connections with ganglion cells located there They also advanced the theory that some of the ganglion cells in the pancreas are sympathetic

The occurrence of receptors in the pancreas resembling Pacinian corpuscles has been reported repeatedly These are particularly abundant in the cat In man, Ceelen (1912) found Pacinian corpuscles in 89 of 100 cases According to his findings, they vary widely in number and distribution, being most numerous on the posterior aspect of the head They occur not only in relation to the blood vessels and the serosa, but also in the parenchymatous tissue Receptors of other types particularly unencapsulated fiber terminations also occur in the pancreas The afferent innervation of the pancreas includes both splanchnic and vagus components

Regulation of Pancreatic Secretion —The secretory activity of the acinous tissue of the pancreas is regulated in part through chemical stimuli (secretin) and in part through nerve impulses As early as 1873, Heidenhain and Landau observed that electrical stimulation of the medulla oblongata brings about an increase not only in the liquid but also in the solid constituents of the pancreatic juice Pavlov (1878) and his students observed that the administration of atropine is followed by inhibition of pancreatic secretion This suggested that the vagus innervation of the pancreas exerts an excitatory influence on its exocrine secretory activity The results of experimental studies carried out by Pavlov s students (Matt, 1894 Kudrewetzky 1894, Modrakowsky, 1906, Babkin and Sawitsch 1908) all support this theory They demonstrated clearly that vagus stimulation augments the production of pancreatic juice Moreover, Kudrewetzky and Modrakowsky have shown that augmentation of pancreatic secretion may also be brought about by sympathetic stimulation, although

by Utterback (1944), afford no evidence that parasympathetic nerves play a part in the innervation of the spleen. Section of the vagi, in his experiments resulted in no change in the numbers of myelinated or unmyelinated fibers in the splenic nerves. Extirpation of the celiac and superior mesenteric ganglia resulted in complete degeneration of all the nerves which enter the spleen. The afferent components of the splenic nerves are mainly myelinated fibers which traverse the splanchnic nerves. Counts of the splenic nerve components in the cat made by Utterback indicate an average of approximately 2000 unmyelinated fibers and an average of approximately 110 myelinated ones, a ratio of approximately 20 to 1. Thus the spleen is supplied with relatively few afferent nerve fibers.

Intrinsic Nerves.—In man the nerves enter the spleen mainly through the hilus. Most of the rami continue into the organ along the arteries. A few ramify in the capsule and give rise to a relatively meager subserous plexus. Within the spleen every nerve, like the vessel which it accompanies, supplies a circumscribed portion of the gland but there is some overlapping of the terminal branches of adjacent nerves (v. Skramlik and Duran-Cao 1925). According to Tait and Cashin (1925), the spleen is divided into a number of zones which correspond to the ultimate branches of the splenic nerves. They also showed that these zones at the same time are nervous and arterial units. The venomotor nerves according to Cleland and Tait (1927), also are distributed to localized parts of the splenic veins. The intrinsic splenic nerves are composed mainly of unmyelinated sympathetic fibers but include visceral afferents most of which are myelinated. The efferent fibers are distributed mainly to the splenic blood vessels and the smooth muscle in the splenic capsule and trabeculae. As the nerves advance into the trabeculae they break up into very delicate strands which in general run parallel to the bundles of smooth muscle fibers. The muscle in the smallest trabeculae seems to be supplied most abundantly (Riegele 1929).

As the arterial branches enter the pulp they are accompanied by slender bundles of nerve fibers which branch according to the branching of the arteries and continue along the smaller arteries including the arterioles. Some nerve fibers also accompany the tributaries of the trabecular veins. Strands of just a few fibers and in some instances individual fibers may be observed adjacent to the inlets and outlets of the sinusoidal spaces in the red pulp where they terminate in relation to contractile cells in the walls of these vessels (Utterback, 1944). These fibers undoubtedly innervate the sphincter mechanisms associated with the sinuses.

Regulation of Splenic Volume Changes and Blood Flow.—Contraction of the spleen in response to sympathetic stimulation had been observed previously, but systematic studies of the effect of nerve stimulation were first undertaken by Bulgak (1877). In his experiments, stimulation of the greater splanchnic nerve, the celiac ganglion or the splenic nerves resulted in contraction of the spleen. The initial phase of this contraction was accompanied by blanching of the organ. This was followed by the appearance of lobulation and rounding off of the angles at the margins. Stimulation of the peripheral end of the cut vagus elicited no apparent reaction in the spleen but stimulation of the central end of the vagus resulted in reflex splenic contraction. The vagus nerve seemed to exert no influence on the spleen. These findings were corroborated by those of

Roy (1881), Schaefer and Moore (1896), and Magnus and Schaefer (1901) None of the latter investigators observed any reaction in the spleen to direct vagus stimulation They therefore concluded that the spleen is innervated only by sympathetic nerves Strasser and Wolf (1905) observed enlargement of the spleen following bilateral section of the greater splanchnic nerve but did not ascribe this result to vagus impulses Physiologic dilatation of the spleen probably is brought about mainly by impulses conducted through the venomotor fibers In the experiments of Cleland and Tait (1927), electrical stimulation of these fibers resulted in engorgement of the spleen corresponding in degree and in duration to the contraction of the splenic vein Section of these fibers abolished reflex dilatation, and the spleen remained in a state of partial contraction following their degeneration On the basis of these results, they concluded that the venomotor fibers constitute the efferent pathway for physiologic splenic dilatation

Spontaneous rhythmic contractions of the spleen have been observed repeatedly In the cat, according to Barcroft Khanna and Nisimaru (1932), the periodicity of these contractions varies between twenty-five and eighty-three seconds, but usually falls between twenty-five and fifty seconds These rhythmic contractions are accompanied by undulatory waves of blood pressure with a corresponding rhythmicity which are related both to the amplitude and the frequency of the splenic contractions but also vary with the general blood pressure Under given conditions the blood pressure changes are proportional not only to the splenic volume changes but also to the volume changes in the circulating blood

A sudden rise in the general blood pressure according to Barcroft and Nisimaru (1932), produces an initial passive dilatation of the spleen which is followed by rhythmic splenic contractions, but a sudden fall in the general blood pressure produces only a passive contraction of the spleen Nerve impulses obviously play no essential part in these reactions since the same results are obtained both before and after denervation of the spleen and removal of the adrenals

Experimental data reported by Grindlay and Herrick (1938) seem to indicate that the volume of the blood circulating through the spleen is not related to the size of this organ but to the state of the blood vascular system as a whole The rhythmic changes in splenic volume are not brought about by rhythmic contractions and relaxations of the splenic musculature but by rhythmic variations in the blood flow In experiments on dogs Grindlay, Herrick and Baldes (1939) found that the waves of arterial blood flow and splenic volume corresponded in period and were synchronous The waves of venous flow corresponded in period but lagged about five seconds behind those of arterial flow and splenic volume The blood flow and splenic volume manifestations of splenic rhythm were not abolished or disturbed by denervation of the spleen The cause of the rhythmic waves of blood flow through the spleen, therefore, appears to be independent of the splenic musculature

Restoration of the splenic circulation after its temporary stoppage also initiates rhythmic contractions of the spleen with or without an intact nerve supply Various other means also may be employed to produce rhythmic splenic contractions For example, the injection of curare causes an initial fall in blood pressure and an increase in splenic volume, followed

by rhythmic splenic contractions The injection of histamine causes an initial fall in blood pressure and a decrease in splenic volume followed by rhythmic splenic contractions The injection of a hemoglobin solution causes a remarkable splenic rhythm which is characterized by a gradual increase in the amplitude of the contractions

In an experimental study of the behavior of the spleen in the dog in hemorrhagic hypotension and shock, Lewis, Werle and Wiggers (1943) obtained data which support the assumption that splenic contraction does not contribute to the elevation and maintenance of arterial blood pressure by virtue of the increased resistance in the splenic shunt but by its augmenting effect on venous return and cardiac output They advanced the opinion that the spleen does not withold blood from active circulation in conditions of shock due to hemorrhage, consequently, if this organ is found large and congested at autopsy, other factors must have been operative

In experiments reported by Farber (1936) the injection of acetylcholine into the splenic artery in the dog resulted in contraction of the spleen, probably due to the direct action of the drug on the splenic musculature The spleen also contracted in response to the stimulating effect of acetylcholine on the extrinsic nerves This response was not abolished by the administration of atropine Ferguson Ivy and Greengard (1936) reported contraction of the spleen in response to intravenous injection of acetylcholine which action was antagonized by atropine They also demonstrated the presence of a splenoconstrictor substance in an extract of the duodenal mucosa which is not identical with acetylcholine histamine or secretin but probably is identical with the substance previously demonstrated in extracts of the duodenal mucosa (Sandblom, Voegtlin and Ivy, 1935) which augments intestinal motility Stephens (1940) showed that contraction of the spleen following the administration of vasodilator substances such as amyl nitrite and glyceryl trinitrite may be passively related to the fall in blood pressure since these substances do not cause contraction of the denervated spleen In their experiments histamine caused contraction both of the normal and the denervated spleen Adrenin produced greater contraction of the spleen immediately after its denervation than before Tyramine produced equal contraction both of the normal and the denervated spleen

Barcroft (1932) reported the results of certain experiments in which necrosis of the skin caused either by friction or high temperature, was accompanied by contraction of the spleen both in intact animals and in animals in which the spleen had been denervated He also reported that estrus pregnancy and lactation are accompanied by contraction of the spleen The splenic contractions associated with estrus and pregnancy are abolished by denervation of the spleen, that associated with lactation is not abolished by splenic denervation Contraction of the denervated spleen associated with necrosis of the skin and lactation and the abolition of splenic contractions associated with estrus and pregnancy by splenic denervation, according to Barcroft, indicates a large humoral element in the causation of the contractions in the former conditions, whereas in the latter conditions the splenic contractions are elicited by nerve impulses

The Thyroid Gland — Extrinsic Nerves —Nerves of both sympathetic and parasympathetic origin extend into the thyroid gland (Fig 62) In man the sympathetic nerves in question arise mainly from the middle cervical

ganglion or the middle cervical portion of the sympathetic trunk. They include fibers which arise in other cervical sympathetic ganglia, particularly the superior cervical. Nonidez (1931) demonstrated the superior cervical origin of some of the nerve fibers which enter the thyroid gland in the dog. A similar anatomical arrangement also has been described in man. The fibers of vagus origin which enter the thyroid gland are mainly components of the superior laryngeal nerve, others are incorporated in the inferior laryngeal nerve. According to Vogt (1931), still other rami enter the thyroid directly from the sympathetic trunks, the common carotid

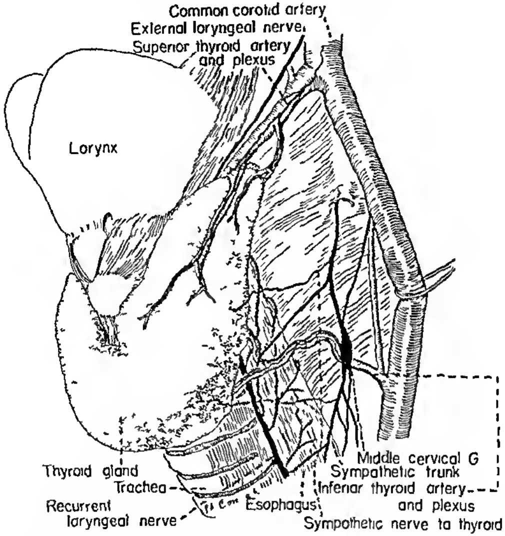


FIG. 6.—Diagrammatic illustration of the extrinsic nerves related to the thyroid gland

subclavian and tracheal plexuses, the glossopharyngeal nerve and the ansa hypoglossi. Some of the sympathetic rami and the nerves of vagus origin which reach the thyroid also include afferent fibers. As the extrinsic nerves approach the thyroid gland most of the rami accompany the superior thyroid artery without becoming intimately incorporated in a plexus.

Intrinsic Nerves.—Within the thyroid gland the nerves in general accompany the branches of the *thyroid arteries*. Some rami also run independently among the thyroid follicles. Most of the *nerve fibers* are unmyelinated but the larger rami include both *large* and *medium-sized* myelinated fibers. Aggregates of autonomic ganglion cells in the superior

laryngeal nerve have been reported by Lemere (1931) and ganglia within the thyroid gland by Nonidez (1911, 1935). The latter investigator also reported the occurrence of scattered neurons in the thyroid of the dog which he regarded as sensory ganglion cells which became displaced from the nodose ganglion of the vagus along the superior laryngeal nerve. He also recognized terminal arborizations in the arterial walls which he regarded as sensory, since they do not lie in contact with the smooth muscle of the media.

Among the early investigators, Kolliker (1855), Peremeschko (1867) and Zeiss (1877) regarded the innervation of the thyroid gland as essentially vasomotor. Most of the more recent investigators who have studied the distribution of the nerves within the thyroid have supported the theory that nerve fibers terminate both in the walls of the blood vessels and in relation to the thyroid follicles. Nonidez (1935) described an interfollicular plexus and nerve fibers ending freely among the follicles but failed to observe nerve fiber terminations in contact with follicular cells. In his preparations most of the follicles were not in contact with fibers of the interfollicular plexus. His data do not indicate a direct innervation of the thyroid gland cells. The interfollicular fiber terminations are regarded as receptive. The innervation of the blood vessels in the thyroid is particularly abundant.

Regulation of Thyroid Function.—Certain early physiologists, particularly Poincare (1875), supported the theory that the innervation of the thyroid includes secretory fibers, although experimental data on which such a theory could be based were not at hand. Of the later physiologic investigators not a few have advanced experimental data which seem to support the theory that thyroid activity is subject to direct nervous regulation; others, on the basis of their experimental findings, could not support this theory. Of the latter group not a few have supported the theory that the secretory activity of the thyroid gland is influenced by its blood supply and, therefore, is regulated indirectly by the vasomotor nerves. Others have attempted to account for the functional regulation of the thyroid gland on the basis of hormonal action.

The vasoconstrictor action of the sympathetic nerves to the thyroid has been amply demonstrated. These nerves probably include vasodilator fibers. The presence of vasodilator fibers in the parasympathetic nerves to the thyroid has not been demonstrated beyond question. Stimulation of the proximal end of the divided vagus results in an increase in the blood volume flow through the thyroid, probably due to an increase in general blood pressure (Mason, Markowitz and Mann, 1930). The blood flow through the thyroid is influenced by reflex stimulation of the carotid sinus nerve which also results in a change in systemic blood pressure. A functional relationship between the thyroid gland and the carotid sinus mechanism, dependent on reflex tonus changes in the vessels of the thyroid, has been pointed out by Rein, Leibermeister and Schneider (1933). They also pointed out that the reflex effects of unilateral carotid sinus stimulation are apparent throughout the entire thyroid gland. The threshold of stimulation by adrenin of the vasoconstrictor endings in the thyroid is definitely lower than that of those in the submaxillary gland (Gunning, 1917). This undoubtedly is significant, in view of the synergistic action of adrenin and thyroxin.

Experimental studies carried out to determine what histologic changes, if any, take place in the thyroid gland following partial or complete deprivation of its nerve supply have not yielded uniform results Katzenstein (1899), following bilateral section of the laryngeal nerves, Lubeke (1902), following section of the laryngeal and pharyngeal nerves Wiener (1909), following unilateral extirpation of the inferior cervical sympathetic ganglion, and Reinhard (1923), following extirpation and stimulation of the cervical sympathetic, reported somewhat indefinite and variable changes, some of which may have been due in part to vasomotor changes following the operative procedure Schilf and Heinrich (1924), Kijono (1925), Vogt (1931) and Reid and Hohman (1936) reported no histologic changes in the thyroid gland, following cervical sympathetic extirpation which they regarded as directly referable to denervation of the gland cells

Experimental studies carried out to determine the effect of nerve stimulation on the thyroglobulin content of the thyroid gland have yielded no definite information regarding the regulation of thyroid secretion Hunt (1923) observed no difference in the effects produced by feeding given quantities of thyroid substance regardless of whether it was prepared before or after prolonged nerve stimulation Hektoen Carlson and Schulhof (1927) by the use of the precipitin reaction also found no difference in the thyroglobulin content of the blood before and after sympathetic stimulation of the thyroid gland These findings in general corroborate the results obtained by Hicks (1926) who compared determinations of the thyroglobulin content of the lymph before and after sympathetic stimulation

Asher and Flack (1911) assumed the existence of secretory fibers in the nerves to the thyroid gland mainly on the basis of the observation that stimulation of the laryngeal nerves brings about the same increased excitability of the depressor nerve and increased effect of adrenin on blood pressure as is brought about by intravenous injection of thyroid preparations Asher and v Rodt (1912) also reported increased excitability of the splanchnic nerves and Ossokin (1914) increased excitability of the vagus nerves during stimulation of the nerves to the thyroid gland Asher and Pfluger (1927) reported the results of experiments which seem to indicate that sympathetic denervation of the thyroid results in diminution of the capacity of the body tissues, particularly the subcutaneous connective tissue and muscles, for absorption

In experiments reported by Asher and Ruetsch (1940), the administration of threshold doses of adrenin in rabbits resulted in a rise in muscle temperature, as measured thermo-electrically Following denervation of the thyroid larger doses of adrenin acting for a longer time were required to produce an equal rise in muscle temperature Following removal of the thyroid still larger doses of adrenin were required to produce a comparable rise in muscle temperature On the basis of all these results, Asher and his collaborators concluded that the secretory activity of the thyroid is regulated at least in part through its sympathetic innervation

In experiments on rabbits reported by Haney (1932) stimulation of the cervical sympathetic trunk by means of an interrupted current for one to three hours was followed by marked rises both in respiration and energy metabolism The rise in respiratory metabolism began on the second day, reached its maximum before the eighth day and returned to normal between

the twentieth and fortieth days. The rise in energy metabolism began on the second day, reached its maximum between the eleventh and fifteenth days and returned to normal between the forty-first and sixtieth days. Since these results did not follow cervical sympathetic stimulation in animals with the thyroid gland removed, the increased metabolism was regarded as the result of increased secretory activity of the thyroid gland due to nerve stimulation.

In experiments reported by Brock, Doty, Krasno and Ivy (1940) cervical sympathetic stimulation after the method of Haney resulted in a[n] appreciable increase in the basal metabolic rate in only one of eight rab[bits]. Complete bilateral cervical sympathectomy in ten rabbits and tw[o] cats resulted in a marked reduction in the basal metabolic rate in seven nine rabbits studied longer than thirty days following operation and both cats.

Neither the results reported by Haney nor those of Brock *et al.* cited above demonstrate the presence of secretory fibers in the sympathetic nerves to the thyroid, since the changes in the secretory activity of the thyroid gland may have been correlated with changes in the thyrotropic activity of the anterior hypophyseal lobe due to the experimental procedures carried out. Experimental data reported by Uotila (1939) support the assumption that the effects of sympathetic stimulation on thyroid activity are exerted mainly through the anterior hypophyseal thyrotropic hormone.

The thyrotropic hormone, according to Krayer (1933), acts directly on the thyroid gland cells. In experiments carried out on rabbits and guinea pigs he observed the same effects of preparations of the anterior hypophyseal lobe on thyroid activity in normal animals and in animals which ha[d] been subjected to bilateral cervical sympathectomy. On the basis of th[e] results obtained in experiments involving removal of the hypophysis a[nd] partial destruction of the tuber cinereum in puppies, Houssay *et al.* (19[..]) advanced the opinion that the hypophysis exerts a constant regulating action on the thyroid by which its normal functional condition is maintained. After hypophysectomy, according to their findings, the thyroid gland enters a transient phase of activity during which the iodine content of the blood is increased and that of the thyroid gland is diminished. This phase of thyroid activity also has been observed in dogs following lesions of the tuber cinereum. A permanent phase of hypothyroidism sets in later during which the iodine content of the thyroid increases and that of the blood diminishes and the basal metabolism is low. According to these investigators, hypothyroidism is etiologically related to hypophyseal insufficiency. The observations of Eitel, Krebs and Loeser (1933) that the hypophyseal thyrotropic hormone induces hypertrophy and hyperplasia of thyroid tissue in blood serum cultures and the finding of Marine and Rosen (1934) that this hormone induces characteristic histologic changes in autotransplanted bits of thyroid tissue are in complete accord with this point of view.

In experiments on guinea pigs reported by Friedgood, Bevin and Uotila (1940) the effect of the anterior hypophyseal hormone was significantly enhanced by combining either adrenin or pilocarpine with it in daily administrations. Their data seem to support the assumptions that the pilocarpine acts through the adrenal medulla and that adrenin increases

the sensitivity of the thyroid cells to the thyrotropic hormone They also concluded on the basis of experimental data, that the administration of thyroid substance results in reduction of the functional activity of the animal s own thyroid via the mechanism through which the secretion of the thyroid hormone is normally regulated

In view of all the data bearing on the regulatory control of the secretory activity of the thyroid gland, it is apparent that hormonal agents, particularly the anterior hypophyseal thyrotropic hormone, play a major role Direct secretory effects of nerve impulses have not been demonstrated beyond question but changes in the blood flow through the gland brought about through the vasomotor nerves and the nervous regulation of the production of the hypophyseal thyrotropic hormone are not unimportant The innervation of the thyroid obviously is not essential for continued thyroid secretory activity under ordinary conditions but certain data emphasize the importance of the sympathetic nerves in the responses of the thyroid to certain situations

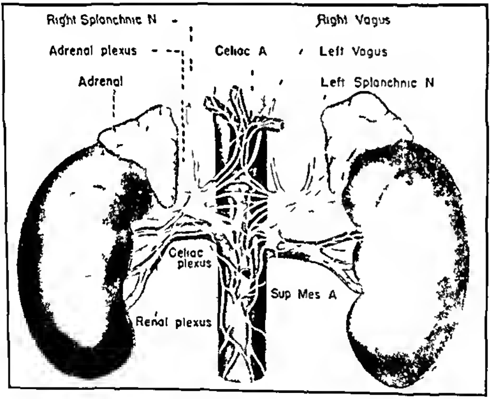


FIG 63 —Diagrammatic illustration of the extrinsic innervation of the adrenals and the kidneys

The Adrenal Glands —Extrinsic Nerves —The innervation of the adrenal gland is derived mainly from the celiac plexus via the adrenal plexus (Fig 63) The latter plexus is continuous with the inferior phrenic plexus superiorly and with the renal plexus inferiorly Its constituent fibers include components of the splanchnic vagus and phrenic nerves and postganglionic axons arising in the celiac ganglia and lesser ganglia located in the adrenal plexus Some splanchnic nerve components join the adrenal plexus or enter the gland directly without passing through the celiac plexus (Biedl, 1897, Renner, 1914, 1931) The splanchnic nerves supply

the major portion of the adrenal innervation. In the cat, according to Hollingshead (1936), Hollingshead and Finkelstein (1937) and Swinyard (1937) the splanchnic fibers in question are derived mainly from the lower thoracic and upper lumbar spinal nerves. According to Young (1939), fibers to the adrenal emerge from the spinal cord from the sixth thoracic to the second or third lumbar segments inclusive, with a few fibers from higher segments in some cases. Most of the efferent fibers which enter the adrenal are preganglionic splanchnic components. A large percentage of the fibers which traverse the adrenal plexus, consequently, are myelinated.

Intrinsic Nerves.—As the adrenal nerves approach the gland many fiber bundles enter the medulla through the hilum; others traverse the adrenal capsule. Many of the fibers incorporated in the latter bundles sweep around the glomerular arches in the outer cortical zone and extend inward in the interfascicular septa. Some of these fibers terminate in relation to blood vessels in the cortex; others extend into the medulla without effecting any terminal connections in the cortex. Since preganglionic fibers extend into the adrenal medulla, a high percentage of the nerve fibers within the gland are myelinated.

Dogiel (1894) described three plexiform structures: one in the adrenal capsule, another in the cortex and a third in the medulla. Renner (1924) recognized these plexuses and expressed the opinion that some of the fibers in the cortical plexus terminate in relation to cortical cells. Alpert (1931) described and illustrated elaborate plexuses in the cortical zones in the human adrenals with offsets of slender fibers which terminate in relation to the cortical cells. Willard (1936) supported the assumption that nerve fibers terminate in relation to some cortical cells but concluded that most of the cortical cells are not directly innervated. Hollingshead (1936), Swinyard (1937) and MacFarland and Davenport (1941) found no conclusive evidence to support the theory that nerve fibers terminate in relation to any of the cortical cells.

Aggregates of ganglion cells have been observed in the capsule of the adrenal gland in various mammals. Ganglion cells in the adrenal medulla also have been reported. MacFarland and Davenport (1941) found no ganglia in the adrenals of the rat. In other mammals they found small ganglia in the capsule and a few ganglion cells in the medulla. Ganglion cells in the adrenal capsule or within the gland probably are sympathetic and represent nerve cells which have been displaced from the primordia of the celiac ganglia. Their axons probably terminate in relation to blood vessels.

The adrenal medulla is abundantly innervated. Nerve fiber terminations in relation to the chromaffine cells have been described repeatedly. Willard (1936) observed terminal structures comparable to boutons in relatively small numbers, which she regarded as too few to represent the chief terminal mechanisms. MacFarland and Davenport (1941) also observed bulbous terminations in small numbers and concluded that the slender fibers which arborize on the surfaces of the chromaffine cells represent the chief terminal mechanisms.

The fibers which terminate in relation to the chromaffine cells, as indicated by the results of degeneration experiments, are preganglionic components of the splanchnic nerves. In Young's (1939) experiments, section of some only of the splanchnic nerve roots resulted in nerve fiber degener-

ation in localized areas of the adrenal medulla. Section of the greater splanchnic nerve resulted in denervation in its anterior half. In the experiments of MacFarland and Davenport (1941) section of the greater splanchnic nerve on either side at the diaphragm, in the rat, resulted in degeneration of 75 to 90 per cent of all nerve fibers in the gland.

In view of the high percentages of nerve fiber degeneration in the adrenal glands caused by incomplete splanchnic nerve section, although the vasomotor fibers are postganglionic, the vagus or parasympathetic nerves can play no important part in adrenal innervation. Although vagus components apparently are present in the extrinsic nerves, the available anatomical data do not support the assumption that the intrinsic adrenal nerves include parasympathetic components.

Innervation of Paraganglia.—Irregular aggregates of chromaffine tissue not incorporated in the adrenal glands frequently occur in relation to the abdominal aorta and the segmental arteries arising from it. This tissue is innervated according to the same mode as the chromaffine tissue in the adrenal medulla. In the cat, dog and rabbit, according to Kofmann (1935), the abdominal aortic paraganglion is connected through strands of nerve fibers with the celiac, adrenal and inferior mesenteric plexuses. These nerves, like the slender rami connected with the minor paraganglia, are made up mainly of myelinated fibers most of which are preganglionic components of the splanchnic nerves which terminate in direct relation to the chromaffine cells (Hollingshead, 1940). The remaining fibers probably are afferent.

Regulation of Adrenal Functions.—The secretory cells of the adrenal cortex, as stated above, probably have no nerve supply. The cortical tissue is known to be capable of secretory activity following complete denervation of the gland. Its regulatory control probably is essentially hormonal.

The secretory activity of the medullary tissue is controlled in a large measure through its sympathetic innervation. Dreyer (1899) reported increased secretory activity of the adrenal medulla in response to splanchnic stimulation. Tschoboksaroff (1910) and Asher (1912) confirmed this observation and pointed out that splanchnic stimulation may elicit increased secretory activity of the medullary tissue independently of changes in the flow of blood through the gland. Data reported by Stewart and Rogoff (1919) confirmed the existence of secretory fibers in the adrenal nerves. According to Gley and Quinquaud (1921), the discharge of adrenin due to splanchnic stimulation is responsible for the second phase in the blood pressure changes produced. The first phase is characterized by an immediate rise in blood pressure due to the direct vasomotor effect of the splanchnic impulses; the second is initiated a little later by the effect of an increased discharge of adrenin into the blood. This finding corroborated the results of certain experiments reported by Tournade and Chabrol (1919) in which an anastomosis was effected between the adrenal vein of a large dog and the jugular vein of a smaller one. Thus the adrenin produced by the gland of the large dog was introduced into the blood of the smaller one. On stimulation of the peripheral end of the splanchnic nerve of the large dog, blood pressure rose immediately in this animal and a little later in the smaller one. Inasmuch as the increased output of adrenin due to splanchnic stimulation could not change the adrenin content of the blood

of the first animal, this result proves conclusively that the rise in blood pressure in this animal was due to the direct vasomotor effect of splanchnic stimulation. The rise in blood pressure which followed in the second animal was due to the increased adrenin content of the blood flowing into its jugular vein from the adrenal vein of the first, brought about by splanchnic stimulation. This represents the second phase in the effect of splanchnic stimulation on blood pressure and proves conclusively that the output of adrenin is increased on sympathetic stimulation of the adrenal gland.

Sympathetic stimulation through the splanchnic nerves commonly results in adrenal hyperemia and an increased outflow of blood from the gland; therefore it may be assumed that the sympathetic supply to the adrenals includes vasodilator fibers. Although splanchnic stimulation does not elicit vasoconstriction in the adrenals, it has been assumed by certain physiologists that the sympathetic supply to this gland includes vasoconstrictor fibers, since the administration of adrenin results in vasoconstriction in the adrenals.

The secretion of adrenin may be influenced reflexly by stimulation of afferent nerves from various parts of the body. Afferent stimulation of somatic nerves commonly elicits increased medulliadrenal secretion. Afferent impulses conducted by either vagus nerve from the regions of the heart and lungs inhibit this secretion, but afferent vagus impulses from the splanchnic area exert no inhibitory influence on the medulliadrenal mechanism (Freeman and Phillips, 1931). The medulliadrenal mechanism also is subject to impulses emanating from the central nervous system. Afferent nerve stimulation, psychic disturbances, or direct injury to the brain may exhaust the adrenin supply. Section of the splanchnic nerves prevents this result. Experimental data reported by Cannon and Rapport (1921) and Jourdan (1934) support the assumption that the medulliadrenal mechanism may be either stimulated or inhibited reflexly through a center located in the floor of the fourth ventricle. Puncture in this area which brings about hyperglycemia also affects adrenal secretion. Indeed the changes in the sugar content of the blood are in part referable to the effect of modified adrenal activity. Takashi (1931) also reported activation of the medulliadrenal mechanism in the dog by injection of peptone, venesection or afferent nerve stimulation following transection of the spinal cord in the lower cervical region. The chemical mediator liberated in the adrenal glands by sympathetic stimulation, according to Feldberg, Minz and Tsudzumura (1933), is not akin to adrenin but exhibits the properties of acetylcholine. According to their view, the secretion of adrenin is brought about by the direct action of this chemical mediator on the medullary cells.

The Bone Marrow.—Anatomic data bearing on the innervation of bone marrow are meager. Nerves comprising both myelinated and unmyelinated fibers enter the marrow cavities with the nutrient vessels. The unmyelinated fibers have generally been regarded as vasomotor and as distributed exclusively to the blood vessels. The myelinated fibers undoubtedly are afferent. Their distribution within the marrow cavity is not fully known. Some undoubtedly are related to the blood vessels, others to the endosteum. Some probably terminate in receptors related neither to the blood vessels nor the endosteum.

The functional relationships of the vasomotor nerves within the bone

marrow undoubtedly correspond to those of other vasomotor nerves. Vasomotor regulation also exerts a regulatory influence on the hemopoietic and other activities of the bone marrow. Certain data also suggest a more direct functional relationship of the hemopoietic tissue to the autonomic nerves.

Observations reported by Samaras (1937) support the assumption that the phagocytic activity of reticulo-endothelial cells in the bone marrow, like that of the corresponding cells in other organs, may be increased due to sympathetic stimulation. The hemopoietic activity of the bone marrow also appears to be subject to modification through sympathetic nerve stimulation. In experiments reported by Somogyi (1938), long continued administration of ergotamine in rats (0.2 mg. per kilo of body weight daily) inhibited blood regeneration following blood loss. Extirpation of the cervical portions of the sympathetic trunks without or including the stellate ganglia resulted in marked decreases in the numbers of erythrocytes and the percentage of hemoglobin and an increase in the number of leukocytes. Faradic stimulation of the cervical sympathetic trunks resulted in increases of 27 per cent in the number of erythrocytes and 23 per cent in the amount of hemoglobin. These responses could not be obtained in animals previously subjected to extirpation of the thyroid gland. In experiments on human subjects reported by Scheer (1940), smoking to the point of signs of intoxication was followed by an increase in the number of reticulocytes in the peripheral blood in most cases. Increased production of these cells was not indicated. The stimulus of nicotine apparently caused their discharge from the bone marrow in increased numbers.

CHAPTER XIII

INNERVATION OF THE URINARY ORGANS

The Kidney.—Extrinsic Nerves.—The innervation of the kidney is derived mainly via the renal plexus which extends from the aortic plexus to the hilum of the kidney along the renal artery. It is made up mainly of rami arising from the celiac ganglia and fibers from the aortic plexus and is joined by the least splanchnic nerve and communicating branches from the adrenal plexus. In some instances, at least one branch of the lesser splanchnic nerve also joins the renal plexus directly. It also receives fibers via one or more slender rami from the lumbar portion of the sympathetic trunk and from the intermesenteric nerves. Direct vagus branches join the renal plexus in many cases. Such branches occur more commonly on the right side than on the left (Renner, 1924). Most of the vagus fibers in the renal supply traverse the celiac plexus. Preganglionic fibers supplying the kidney are present in all the splanchnic nerves. The afferent fibers are mainly components of the tenth, eleventh and twelfth thoracic nerves (Fig. 64).

The renal plexus shows a wide range of variation in the configuration of the nerve fiber bundles which compose it and in the distribution of its ganglia. In cases in which the ganglion cells in the celiac plexus are not all incorporated in one or two ganglia, not uncommonly there is a ganglion in the renal plexus near the origin of the renal artery. This may be regarded as the first renal ganglion. The renal plexus usually comprises one or more additional ganglia located nearer the hilum of the kidney. These usually occur at nodal points in the plexus. Renner (1924) also found ganglion cells either singly or in very small groups in preparations of the renal plexus at points where no ganglionic enlargements were apparent. Such cells may occur at nodal points or in the courses of fiber bundles.

Intrinsic Nerves.—The nerves which enter the kidney from the renal plexus accompany the renal artery and its branches around which they form plexuses. Even after the arteries enter the renal parenchyma nerve fiber bundles may still be observed macroscopically along their walls. The intrinsic nerve plexuses commonly divide at the bifurcation of the arteries and continue along even the smaller arterial branches. In favorable microscopic preparations, nerve fibers may be observed in relation to arterioles and capillaries. Afferent nerve fiber terminations also have been described in the kidney, particularly in the musculature of the renal pelvis, the adventitia and media of the renal vessels, and the renal capsule (Renner, 1924).

The nerve fibers in the parenchyma are mainly unmyelinated and of small caliber. Renner (1924) observed very few small myelinated nerve fibers in the renal parenchyma although myelinated fibers occur in greater abundance in the region of the renal calyces and in the renal pelvis. According to Hubler (1922), the renal calyces are richly supplied with unmyelinated nerve fibers which terminate in relation to the musculature, including the smooth muscle fibers which he claimed to have observed in the renal calyces above the sphincter papillae. The early investigators

quite generally supported the assumption that the renal tubules are directly innervated Hirt (1926) and Kaufman and Gottlieb (1931) also interpreted their findings as supporting this point of view, but unmistakable nerve fiber terminations in contact with parenchymal cells have not been demonstrated

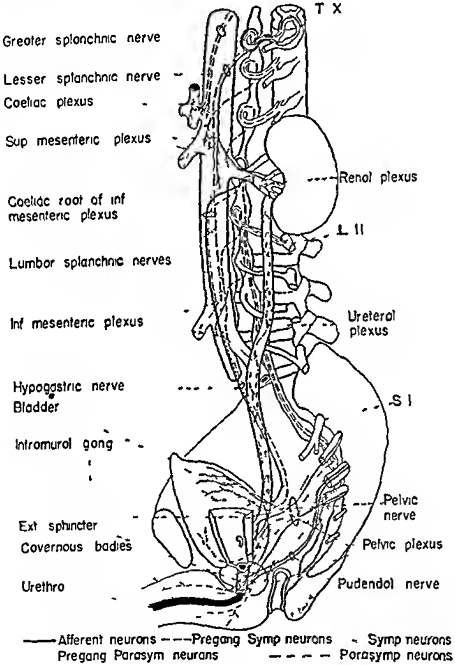


Fig 64 —Diagrammatic illustration of the innervation of the urinary organs

Regulation of Renal Functions —Function of the Renal Nerves —According to many investigators, including Cushny (1917), Millikin and Karr (1925) and Gubergritz and Itschenko (1926), the function of the renal nerves is essentially vasomotor They regard the splanchnic supply to the kidney as including many vasoconstrictor and few vasodilator fibers but no secretory fibers Since splanchnic stimulation results in constriction of the renal blood vessels with diminution of the volume of blood flowing through

the kidney and diminution in the output of urine and section of the splanchnic nerves results in dilatation of the renal blood vessels with increased output of urine it seems unnecessary to assume the existence of renal secretory fibers in the splanchnic nerves Certain data seem to support the theory that the vagus nerves convey secretory fibers to the kidneys but these cannot be regarded as conclusive

Denervation of the kidneys is not incompatible with life As has been shown experimentally, excretion may continue many months, perhaps indefinitely after all connections of the kidney with the central nervous system have been divided Claude Bernard (1859) showed that secretion of urine by the affected kidney is increased following unilateral section of the splanchnic nerves in the dog This was confirmed by the work of Eckhard (1869) Grek (1912), Rhode and Ellinger (1913), Jungmann and Meyer (1913) and not a few later investigators Carrel and Guthrie (1906) transplanted the kidneys of one dog into another and kept the latter animal alive for many days after removal of its own kidneys In this case, the kidney function obviously was carried out in the absence of direct nervous regulation

The first detailed study of the function of the kidney after transposition was carried out by Lobenhoffer (1913) In his experiments the pedicle was severed and the kidney was transposed to the splenic vessels On the basis of his results he concluded that a kidney transposed in this manner is able to meet the ordinary demands of life Zaayer (1914) reported the case of a dog which lived six years following transposition of its single kidney to the iliac vessels Dederer (1918) transposed the left kidney of a dog to the vessels of the neck and two weeks later removed the right kidney The dog remained alive and well for more than four months after removal of the right kidney Phenolsulphonphthalein was excreted rapidly by the transposed kidney and its output of urine was markedly increased following removal of the other kidney In another experiment Dederer (1920) homotransplanted a kidney and an ovary from one dog to another of the same litter The dog with the transplanted kidney died of distemper twenty-six days later Examination of the transplanted kidney showed that it reacted to the severe constitutional infection, distemper, in a manner similar to that of the animal's own organs In this case the transplanted kidney could have had no nerve connections, yet, although the animal had two kidneys of its own, phenolsulphonphthalein appeared in the urine of the transplanted kidney two minutes and forty seconds after its intravenous injection

Quinby (1916) reported the results of a large number of experiments carried out on dogs in which the kidney on one side was removed and then reimplanted by anastomosing the severed vessels and the ureter According to Quinby stripping of the renal vessels of nerve fibers is not sufficient to insure complete denervation of the kidneys because a few nerve fibers are actually within the vessel walls In one series of animals the ureters were brought out through the flanks two days to three weeks after the primary operation, and the urines were collected and compared In this series the output of both liquid and salt was increased, and this increase persisted ten to fourteen days On the normal side, the flow of urine was temporarily inhibited by handling the ureter Such temporary inhibition was not apparent on the opposite side, but urine flowed from the denervated

kidney as soon as the ureter was opened. In another series of animals the normal kidney was removed five days to two weeks after the primary operation. The capacity of the single denervated kidney to eliminate following intravenous injection of normal salt solution, lactose solution and phenolsulphonphthalein was compared with that of a normal dog which had been subjected to unilateral nephrectomy. In a third series of animals, Quinby (1917) tested the response of the denervated kidney to intravenous injection of hypertonic solutions of sodium chloride, urea and caffein and found that the reactions of the normal and the denervated kidney to these solutions were practically identical. These findings strongly suggest the absence of secretory fibers to the kidney.

Marshall and Kolls (1919–1920), who made a most painstaking study of the results of denervation of the kidney in relation to diuresis and urinary secretion, agreed with Quinby that depriving a kidney of its nerve supply results in an increased output of urine on that side with a relative lowering but total increase of solids. They found that the increased excretion of urine by the denervated kidney persisted for months after the operation, whereas Quinby had reported that it persisted for only ten days to two weeks. On the basis of their experimental results, they concluded that the changes noted in the secretory activity of the denervated kidney were due solely to vasodilatation with the consequent increased flow of blood through the organ. When the renal artery was constricted by artificial means after denervation of the kidney, the output of urine was correspondingly reduced. They also found that when the denervated kidney was secreting much more urine than the normal kidney, the normal ratio could be reestablished by paralyzing the splanchnic on the normal side.

The results obtained by Milliken and Karr (1925) in general corroborate those of Marshall and Kolls. They also afford additional evidence that denervation of both kidneys, in experimental animals (dogs), as far as this is possible by cutting all the visible fibers of the renal plexus, produces no untoward results and that the animal may continue to live in good health for an indefinite period. Gubergritz and Itschenko (1926) also found no positive evidence in support of the theory that renal secretory activity is regulated either in whole or in part through secretory fibers.

In experiments reported by Grabfield and Swanson (1939), in which sodium chloride was added to the diet of dogs which had been subjected to denervation of one kidney, the excretion of the salt by both kidneys occurred more promptly than in normal dogs. They interpreted this result as indicating a coordinating mechanism of humoral nature affecting both kidneys which probably is associated with the renal nerves.

In a study of renal circulation and secretion in dogs, with special reference to the effect of extracts of the posterior hypophyseal lobe, Handovsky and Samaan (1937) found that the renal blood flow is constant within narrow limits in the resting animal and is diminished for a brief period when the animal is disturbed. Diuresis produced by administration of water was preceded by an increase in renal circulation which was independent of nerve impulses and unrelated to changes in systemic blood pressure. Unilateral section of the splanchnic nerves resulted in increased renal circulation and secretion in the affected kidney. Administration of adrenin caused a decrease in renal circulation and secretion, depending on the dosage, but the output of urine returned to the normal level in ten to

twenty minutes. The effect of adrenin was more pronounced after ingestion of water. In conscious dogs with water diuresis the administration of posterior hypophyseal extract resulted in a decrease in the output of urine, although the renal blood flow remained almost constant. Large doses produced a marked antidiuretic effect in unanesthetized animals. In anesthetized animals large doses produced a diuretic effect. In both instances renal circulation showed an initial reduction followed by a prolonged increase.

In a series of experiments carried out by Asher and Pearce (1913), the entire renal nerve supply on one side was anesthetized by the local application of a concentrated solution of phenol. The splanchnic nerves on the opposite side were divided. Following decerebration of the animal, the vagus on this side was subjected to intrathoracic stimulation for varying periods. During these periods the quantity of urine secreted by the kidney in question was increased, while that secreted by the other kidney remained unchanged. The urine secreted under vagus stimulation differed from that secreted by the other kidney during the same period in that its solid contents were markedly increased. They concluded, therefore, that vagus stimulation exerts a true secretory effect on the kidney. These findings were corroborated by those of Mauerhofer (1913) but the results of later experiments carried out by Pearce and Carter (1915) did not fully confirm the earlier results reported by Asher and Pearce. Kusakari (1930) on the basis of the results of experiments involving the injection of phenol sulphonphthalein and section of the vagus nerves concluded that vagus impulses probably have no effect either on the quantity or quality of the urine excreted.

Following section of the vagus nerves, Jungmann and Meyer (1913) observed diminution in both the quantity of urine secreted and its solid constituents. Occasionally they observed an increase. This suggested to them that the vagus under certain conditions may exert an inhibitory influence on renal secretion. According to Ellinger (1921), the vagus supply to the kidney includes fibers which augment diuresis without increasing the quantity of urine. Nakazawa (1924) observed an increase in the nitrogenous constituents of the urine following vagus section. Consequently he concluded that the vagus includes fibers which inhibit the nitrogen output.

Rhode and Ellinger (1913) and Jost (1914) suggested that the splanchnic nerves also convey fibers which exert a direct secretory influence on the kidney. Ellinger (1921) later maintained that the splanchnic fibers accompanying the renal artery exert an inhibitory influence on the excretion of both water and the solid constituents of the urine. He maintained that the effect of the vagus and splanchnic nerves is the same on the excretion of water but opposite on the excretion of the solid constituents of the urine. According to Ellinger and Hirt (1925), the greater splanchnic nerve augments the output of ammonia while the fibers leaving the sympathetic trunk in the lower thoracic and lumbar segments inhibit it. The lower fibers also inhibit the output of phosphates but augment slightly the total nitrogenous output. On the other hand, the greater splanchnic nerve inhibits the total nitrogenous output but augments the output of phosphates. They also pointed out that the vagi and the splanchnics are mutually antagonistic in their effect on diuresis. When the lesser splanch-

nic was divided before section of the vagus, in their experiments, the output of urine following vagus section was greatly increased due to the absence of vasoconstriction. On the other hand, when vagus section was carried out first, the output of urine following section of the lesser splanchnic was also greatly augmented. These results were due in a large measure to vascular changes but, as demonstrated by Asher (1915) and his students, the vagus supply to the kidney includes no vasomotor fibers nor does vagus stimulation result in renal vasodilatation.

In experiments reported by Kusakari (1930), in which the rate at which phenolsulphonphthalein previously injected was excreted by the kidneys was determined, it was found that both water and the drug were excreted in equal quantities by both kidneys while the nerves were intact. Following section of one splanchnic nerve, the output of urine by the kidney on the corresponding side was increased but the rate at which the drug was excreted remained practically unaltered. This result was interpreted as indicating an influence of splanchnic impulses on the resorptive activity of the renal tubules. The effect of caffein on the renal functions, in Kusakari's experiments, was not appreciably influenced by section of either the vagus or splanchnic nerves. This drug apparently inhibits resorption by its direct action on the cells of the renal tubules.

In experiments reported by Muller, Petersen and Rieder (1930), the normally innervated kidneys of the dog gave no evidence of damage for about thirty minutes following heavy injections of Bacillus coli but, with the onset of a chill, albumin, red blood cells and bacteria appeared in the urine very promptly. In animals with one kidney previously denervated, this kidney continued to excrete normal urine after the injection of the bacteria in spite of the chill, whereas, with the onset of the chill, the urine from the normally innervated kidney promptly showed the presence of albumin, red blood cells and bacteria in large quantities. According to Milles, Muller and Petersen (1931), denervation of the kidney in the dog is followed by general dilatation of the renal vascular bed and some degenerative changes, particularly in the intima of the blood vessels.

Certain of the experimental results reported above suggest that renal secretory activity is influenced to some extent by nerve impulses acting directly on the kidney cells. The output of both water and the solid constituents of the urine, however, is determined mainly by the volume of blood flowing through the kidney. In view of the fact that denervation of both kidneys, in experimental animals, is not necessarily followed by untoward results, and in view of the volume of experimental data which seems to indicate that the renal output is determined solely by the volume and content of the blood flowing through the kidney, the burden of proof must still rest with those who maintain that the kidney is supplied with true secretory fibers.

Reflex Regulation of Renal Function.—The secretory activity of the kidney is subject to reflex nervous regulation in some degree. Local cooling of the skin in the lumbar region results in inhibition, while increasing the cutaneous temperature in this region results in augmentation of renal secretion. These functional changes are due mainly to reflex vasomotor changes in the kidney. Cold applications to the skin of an experimental animal result in an appreciable decrease in the size of the kidney and diminution of pressure in the renal vein. Similar reduction in the size of the kidney may also be

brought about by afferent stimulation of a peripheral nerve, *e g*, the sciatic or an intercostal nerve Reflex inhibition of renal function elicited by impulses arising in some other part of the urinary system is not uncommon Renal colic frequently is accompanied by anuria which may persist for hours or even days, due to reflex spasm of the renal arteries The same result may be brought about by kinking or compression of the ureter Pflaumer (1919) was unable to elicit any effect on renal secretion by mechanical stimulation of the mucosa of the ureter On the other hand, he observed inhibition of renal secretion as the internal pressure of the urinary bladder became increasingly greater (vesico-renal reflex) Ureteral stasis also inhibits the output of urine (uretero-renal reflex) According to Blatt (1930), stimulation of the lower third of the ureter also elicits reflex volume changes in the kidney on the opposite side Direct warming or cooling of one kidney usually elicits no reaction in the other but strong thermal stimulation of the one usually calls forth a reflex response in the other Lebelhor (1936) reported clinical cases in which marked diminution of the urinary output of an apparently normal kidney was associated with a lesion of the other kidney On the basis of results obtained in animal experiments, he concluded that the output of the normal kidney was limited by reflex vasoconstriction elicited by the stimulating effect of the lesion in the contralateral organ

Central Regulation of Renal Function —Claude Bernard observed polyuria following a lesion in the floor of the fourth ventricle between the vagus and vestibular nuclei Meyer and Jungmann (1913) produced a lesion in the floor of the fourth ventricle which resulted in an increase in the output of urine but in a proportionately greater increase in the sodium chloride output which did not affect the salt content of the blood, even though the animal had previously been rendered salt poor This result of the lesion was not observed following section of the splanchnic nerves The efferent impulses involved obviously are carried out over these nerves According to Jungmann (1922), puncture of the center for carbohydrate metabolism in the medulla results in diuresis with increased elimination of sodium chloride independently of its effect on the sugar content of the blood

The above results probably could be explained on the assumption that a lesion in the region of the carbohydrate center involves fiber tracts which mediate impulses which are conducted via the splanchnic nerves to the kidney as well as to the liver Dresel (1922) presented evidence which he interpreted as indicating that the effects on renal secretion of lesions in the medulla are not the results of injuries to fiber tracts but to medullary centers In collaboration with Brugsch and Lewy, he found a region medial to the spinal tract of the trigeminal nerve, ventromedial to the restiform body and dorsal to the nucleus of the facial nerve which he regarded as the center which regulates both the elimination of water and sodium chloride

Polyuria occurs not uncommonly as an accompaniment of epileptic seizures and violent attacks of migraine It also accompanies certain psychic states *e g*, expectancy or fright These effects undoubtedly are mediated through hypothalamic autonomic centers and the efferent pathways leading from these centers to the cells of origin of the splanchnic nerves The role of hypothalamic centers in water metabolism is discussed more specifically in Chapter IV

Although nerve impulses play no important role in renal secretion, this

rôle must be regarded as only regulatory and dependent on the vasomotor control of the renal blood vessels exerted through the sympathetic nerves Renal function is determined mainly by the inherent capacity of the renal elements, the hydrostatic relationship of the blood to the kidney and the stimuli to the renal secretory elements afforded by substances in the circulating blood

The Ureter —Nerve Supply —The ureter derives its nerve supply mainly from the renal spermatic (or ovarian) and hypogastric plexuses (Fig 64) A subordinate plexus derived from the vesical plexus also surrounds its lower portion The afferent fibers supplying the ureter are mainly components of the eleventh and twelfth thoracic and first lumbar nerves Its vagus supply probably also includes afferent components

The arrangement of the nerves in the wall of the ureter seems to be relatively simple The majority of the fiber bundles run longitudinally but branch freely and intercommunicate with one another In man and certain other mammals, particularly dogs and cats, groups of ganglion cells are associated with the intrinsic nerves in the lower third of the ureter Ganglion cells have not been observed in the upper two-thirds of the ureter in any animal The sympathetic and parasympathetic components of the nerves to the ureter cannot be differentiated anatomically, but it is highly probable that the ganglion cells in the lower third are incorporated in parasympathetic efferent chains Most of the intrinsic nerve fibers are unmyelinated and of small caliber

Control of the Ureteral Musculature —The musculature of the ureter, like other smooth muscle possesses the inherent capacity to undergo rhythmic contractions Rhythmic peristalsis plays an important part in propelling the renal secretion toward the bladder Such contractions of the ureter persist, in the intact animal, following section of all its extrinsic nerves Under proper conditions they can be elicited in excised pieces of the ureter Ureteral activity under normal conditions, probably is subject to nervous regulation If, in an experimental animal, the kidney is actively secreting peristaltic waves of contraction may be observed which are propagated along the ureter from the kidney to the urinary bladder in regular sequence Direct stimulation of the ureter at any point gives rise to a contraction wave which is propagated in both directions from the point stimulated thus peristalsis and antiperistalsis may be observed at the same time (Schulf, 1926)

Engelmann (1869) advanced the opinion that the musculature of the ureter is stimulated automatically to undergo periodic contractions and its functional regulation requires neither intrinsic ganglion cells nor extrinsic nerves Hryntschak (1925), and others adopted this point of view The abundant nerve supply to the ureter, however, cannot be regarded as devoid of functional significance

The data obtained in experiments involving direct stimulation of the nerves to the ureters are not unequivocal For example Fagge (1902) and Stern (1903) observed acceleration of ureteral contractions in response to stimulation of the hypogastric nerve Elliot (1906 1907) observed a similar response in certain mammals but failed to obtain it in the ferret Wharton and Hughson (1931) advanced the opinion that the ureteral musculature is activated by sympathetic stimulation but they observed no response of this musculature to sacral parasympathetic stimulation On

the basis of an extensive review of the literature, including the reports of studies of the effects of various drugs on the ureteral musculature, Gruber (1933) concluded that, although the results of many of the reported studies are inconclusive, the data available support the assumption that the sympathetic innervation of the ureter includes both excitatory and inhibitory fibers, the parasympathetic innervation only excitatory fibers

The lower end of the ureter is not provided with a special sphincter muscle Its opening and closing appear to be regulated by the activity of the bladder musculature and the internal vesical pressure According to the current teaching, contraction of the bladder tends to close the ureter so that urine cannot be forced back into it while the bladder is expelling its contents Contraction of the bladder probably also results in reflex contraction of the lower portion of the ureter This also would tend to prevent the back flow of urine into the pelvis of the kidney Maintenance of the tonus of the ureteral musculature and reflex coördination of the activities of the ureter to contractions of the bladder probably represent the most important functions of the nerves supplying the ureter

The Urinary Bladder —Extrinsic Nerves — The urinary bladder is innervated through the vesical plexuses which are complex meshworks of nerve-fiber bundles and flattened ganglia extending from the region of the trigone along the lateral aspects of the bladder Each vesical plexus may be regarded as a subdivision of the corresponding pelvic plexus It receives preganglionic and visceral afferent fibers via both the hypogastric and pelvic nerves The pudendal nerve through which the external vesical sphincter is supplied, also conveys afferent fibers to the internal vesical sphincter and adjacent parts of the bladder (Fig 61)

Most of the sympathetic preganglionic fibers involved in the innervation of the bladder terminate in the ganglia in the vesical plexus some probably terminate in the lumbar ganglia of the sympathetic trunk In the dog according to Schabadasch (1928), a large percentage of the extrinsic fibers enter the bladder wall without synaptic relays in extrinsic ganglia The ganglia in the vesical plexus are neither exclusively sympathetic nor exclusively parasympathetic, but preganglionic fibers of both the thoracolumbar sympathetic and the sacral parasympathetic outflows effect synaptic connections in them (Kuntz and Moseley, 1936)

Intrinsic Nerves — The nerves which penetrate the bladder wall from the vesical plexus join the intramural plexus which includes numerous ganglia The intramural ganglia are most abundant in the trigone and gradually become less abundant as the distance from the trigone increases The fundic area probably is devoid of ganglia The larger intramural ganglia and some of the smaller ones are situated just beneath the serosa Other small ganglia are located between muscle bundles (Wolhynski, 1930) but relatively few lie deeply imbedded in the muscle The intramural ganglia, like those of the vesical plexus, receive preganglionic fibers via both the hypogastric and the pelvic nerves In experiments carried out on cats Moseley (1936) found that approximately 40 per cent of the intramural ganglia receive preganglionic fibers exclusively via the hypogastric nerves (sympathetic outflow), approximately 40 per cent exclusively via the pelvic nerves (parasympathetic outflow) and approximately 20 per cent via both the hypogastric and the pelvic nerves Although the number of ganglia which, according to their preganglionic connections, must be classified as

sympathetic is approximately equal to the number which, by the same criterion, must be classified as parasympathetic, there is a preponderance of parasympathetic ganglion cells in the bladder wall, since most of the larger ganglia are parasympathetic. Most of the ganglia which receive preganglionic fibers via both the hypogastric and the pelvic nerves also are relatively small.

Most of the nerve fibers in the bladder wall are unmyelinated and of small caliber. Myelinated fibers also occur. Of the latter, those which penetrate deeply into the wall undoubtedly are afferent. Nerve fiber terminations in the mucous membrane which presumably are afferent have been described by various investigators. According to Schabadasch (1934), afferent terminations in the mucosa are limited to the area of the trigone. According to Langworthy and Murphy (1939), receptors are widely distributed in the mucosa and submucosa but most of those in the trigone and adjacent areas are connected with afferent fibers which traverse the sympathetic nerves, whereas those farther removed from the base of the bladder are connected with afferent components of the pelvic nerves. Kleyntjens and Langworthy (1937) demonstrated complex terminal arborizations of relatively large afferent fibers in the musculature of the bladder, which they interpreted as stretch receptors since, in their experiments, the bladder did not respond normally to stretch following section of the dorsal sacral nerve roots. The histologic structure and the distribution of the stretch receptors in the muscle have been studied further by Langworthy and Murphy (1939) in methylene blue preparations. They also studied the distribution of the sympathetic and parasympathetic motor endings in the bladder musculature and advanced the opinion that the efferent innervation of the detrusor muscle is effected solely through parasympathetic fibers, whereas the sympathetic fibers in the bladder wall are distributed mainly to the blood vessels, Bell's muscle and the crista of the urethra. Contrary to these findings, abundant physiologic data support the assumption that the detrusor muscle also is innervated through sympathetic fibers.

Innervation of the Urethra.—The male urethra is innervated through the prostatic and cavernous plexuses, both of which are subsidiaries of the pelvic plexus. They include sympathetic fibers derived from the hypogastric plexus and parasympathetic fibers derived from the pelvic plexus. The prostatic plexus is continuous with the vesical plexus and lies in intimate contact with the prostate gland. It supplies fibers to the neck of the bladder, the prostate and the prostatic urethra. The cavernous plexus may be regarded as the forward extention of the prostatic plexus. Nerves arising from the cavernous plexus supply the corpora cavernosa penis and, communicating with branches of the pudendal nerves, give off rami to the corpus cavernosum urethræ and the penile portion of the urethra.

The female urethra is innervated through the vaginal plexus which is composed mainly of parasympathetic fibers derived from the pelvic plexus but includes some sympathetic fibers derived from the hypogastric plexus and in part directly from the sacral segments of the sympathetic trunk. The external vesical sphincter and the compressor urethræ muscles are innervated through the pudendal nerves.

Regulation of Vesical Function.—**Specific Actions of Sympathetic and Parasympathetic Nerves.**—The urinary bladder is a muscular organ whose functions are storage of the renal secretion and its periodic discharge. Its

musculature consists mainly of three layers the components of which are so intimately interwoven that they constitute a functional unit the detrusor muscle Its outlet is provided with an internal sphincter composed of smooth muscle and an external sphincter composed of striated muscle The smooth muscle, including the internal sphincter, is innervated through both sympathetic and parasympathetic nerves, the external sphincter through somatic nerves

In general stimulation of the parasympathetic innervation of the bladder results in functional activity, and stimulation of the sympathetic nerves in inhibition of function Under certain conditions, these common responses to parasympathetic and sympathetic stimulation may be reversed In experiments on cats reported by Langworthy, Kolb and Lewis (1940) sympathetic stimulation caused an initial rise in intravesical pressure followed by a fall below the normal resting level, when the volume was held constant, and an initial decrease in the vesical volume followed by an increase, when the intravesical pressure was held constant Stimulation of the hypogastric nerves also resulted in closure of the ureteral orifices and their displacement toward the mid line The base of the bladder also was drawn caudalward by the contraction of Bell's muscle Following sympathetic denervation of the bladder it accommodated a smaller volume of liquid before micturition occurred

Unilateral stimulation of the pelvic nerve elicits contraction of the corresponding lateral half of the detrusor muscle without materially affecting the other half If one pelvic nerve has been cut several weeks previously, stimulation of the intact nerve results in contraction of the entire bladder musculature (Elliott, 1906, 1907) Bilateral section of the pelvic nerves results in marked atony of the detrusor muscle and closure of the sphincter (Denning, 1924) The liquid content is held at higher pressure than in the normally innervated bladder and for the first few days the vesical capacity is increased but drops somewhat below the normal level when automatic micturition begins (Langworthy, Reeves and Tauber 1934) The emptying reflex then is initiated earlier, in response to filling of the viscus, than in the normally innervated bladder

In a study of the action potentials of the nerves of supply to the bladder in the cat, Evans (1936) obtained no satisfactory evidence that the sympathetic nerves play any part in vesical function Langworthy, Kolb and Lewis (1940) advanced the opinion that the detrusor muscle is devoid of functional sympathetic innervation Their finding that sympathetic stimulation results in an initial rise in intravesical pressure followed by a fall below the normal level, if the volume is held constant, and an initial decrease in volume followed by an increase, if the pressure is held constant probably could be explained as due to the reactions of the muscles at the base of the bladder i e, Bell's muscle and the crista of the urethra, which they concede are sympathetically innervated

In experiments on cats and dogs reported by Kuntz and Saccomanno (1944), in which the responses of the musculature near the apex of the bladder to sympathetic stimulation were recorded under conditions calculated to eliminate any effects on the records of responses of the musculature at the base of the viscus, faradic stimulation of the hypogastric nerves elicited an initial contraction followed by prolonged inhibition Functional sympathetic innervation of the detrusor muscle, consequently, is

demonstrated In these experiments, the initial contraction elicited by moderate sympathetic stimulation was of short duration and small amplitude The following relaxation was prolonged but usually not very marked (Fig 65) The results of experiments carried out on male human subjects under spinal anesthesia, which, with respect to the sympathetic innervation of the bladder, are comparable to those cited above, have been reported by Learmonth (1931) In general, his findings corroborate those cited above Stimulation of the entire sympathetic supply to the bladder results in powerful contraction of the ureteric orifices, increased tonus in the trigone and contraction of the internal vesical sphincter, but no observable effect on the detrusor muscle although this muscle is inhibited Stimulation of either hypogastric nerve results in contraction of the ureteric orifice on the same side, increased tonus in the trigone and contraction of the internal sphincter No reflex responses in the bladder could be elicited by stimulation of the proximal portion after section either of one hypogastric nerve or the entire sympathetic supply The immediate results of section of the sympathetic supply are relaxation of the ureteric orifices, the entire trigone

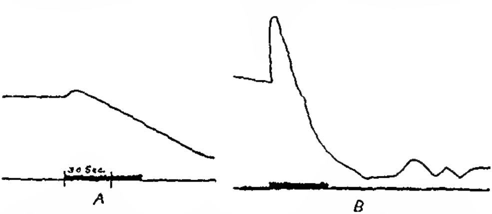


FIG 65 —Kymographic records showing initial contraction of the detrusor muscle followed by prolonged inhibition in response to moderate (A) and strong (B) stimulation (Kuntz and Saccomanno 1944)

and the internal sphincter but no observable change in the detrusor muscle After an interval of about twenty-one days, the ureteric orifices close in the intervals between jets of urine, the trigone appears less relaxed but still abnormal, and the internal sphincter may close completely, although it offers less resistance than the normally innervated sphincter to the advancing beak of the cystoscope Intravenous injection of adrenin in appropriate dosage in Learmonth's experiments, resulted in an immediate active dilatation of the bladder which remained at its increased capacity for approximately five minutes This result definitely indicates the existence of inhibitory fibers in the sympathetic supply to the detrusor muscle in man

On the basis of experimental studies carried out on dogs, Henderson and Roepke (1934) advanced the hypothesis that the functional activity of the bladder involves both a tonic and a contractile mechanism Tonic stimulation in their experiments, resulted in liberation of an acetylcholine-like substance The tonic mechanism, furthermore, was depressed by atropine Contractile stimulation did not result in liberation of an acetylcholine-like substance and the contractile mechanism was not depressed by atropine

In experiments on cats reported by Mellanby and Pratt (1940), instantaneous change from constant intravesical pressure to constant volume conditions caused either an isometric contraction or a state of quiescence at zero pressure, according to the phase of isotonic rhythm at which the change was made. The isometric contraction was followed by a state of quiescence at zero pressure for an indefinite period or by a series of similar rhythmic contractions. Division of the pelvic nerve abolished the isometric contractions. Stimulation of its peripheral portion elicited maximal isometric contractions. Acetylcholine elicited prompt responses similar to isometric contractions. Adrenin elicited similar responses after a long latent period. Atropine abolished the isometric contractions more readily than it destroyed the isotonic rhythm.

Micturition.—Normal micturition is in part reflex and in part a voluntary act. The nervous mechanism through which the voluntary control of this function is exercised has engaged the attention of not a few investigators. According to Müller (1918) and Adler (1918), the cortical impulses involved in voluntary micturition are not conducted to the bladder musculature directly but to the external sphincter which is a voluntary muscle. The peripheral fibers through which these impulses are conducted are components of the pudendal nerve. Their direct effect is relaxation of the external sphincter. According to the theory advanced by Müller, relaxation of the external sphincter gives rise to stimuli which are conducted back to the spinal cord via the afferent pudendal fibers which effect reflex connections with efferent components of the pelvic nerves, i. e., the micturition reflex is initiated by voluntary inhibition of a striated muscle and then carried out as a spinal reflex through the appropriate visceral efferent chains like the spinal reflexes involved in the functional control of other visceral organs.

On the basis of experimental studies carried out on cats Barrington (1914–1921) described a series of five micturition reflexes. (1) A hind-brain reflex through which contraction of the detrusor muscle is elicited by distending the bladder. Both the afferent and efferent pathways involved in this reflex traverse the pelvic nerves. (2) A hind-brain reflex through which contraction of the detrusor muscle is elicited by running water through the urethra. The afferent pathway of this reflex traverses the pudendal, and the efferent pathway the pelvic nerve. (3) A spinal reflex through which a slight transitory contraction of the bladder is elicited by distending the proximal urethra. Both afferent and efferent limbs of the reflex arcs employed traverse the hypogastric nerves. (4) A spinal reflex through which relaxation of the urethra is elicited by running water through it. Both afferent and efferent limbs of the reflex arcs employed traverse the pudendal nerves. (5) A spinal reflex through which relaxation of the urethra is elicited by distending the bladder. The afferent limbs of the reflex arcs employed traverse the pelvic, and the efferent limbs the pudendal nerves. Still another spinal micturition reflex has been described by Barrington (1931) through which relaxation of the smooth muscle, particularly of the proximal third of the urethra, is elicited by distending the bladder. Both the afferent and efferent limbs of the reflex arcs employed in this reflex traverse the pelvic nerves. In decerebrate animals according to Barrington, distention of the bladder through filling elicits reflex contraction of the detrusor muscle. This in turn elicits reflex relax-

ation of the urethra, which elicits further contraction of the detrusor muscle, resulting in complete emptying of the bladder The reflexes are carried out in part through spinal cord centers and in part through centers in the brain stem

In later experimental studies carried out on decerebrate cats, Barrington (1942) found that the mean rate at which urine passes through the urethra in normal micturition is greater than necessary to elicit reflex contraction of the detrusor muscle On the basis of all his pertinent data he concluded that urethral stimulation by liquid passing through it may elicit contraction of the detrusor muscle through a hind-brain reflex carried out through afferent components of the pudendal and efferent components of the pelvic nerves or through a spinal reflex carried out through afferent and efferent components of the pelvic nerves The former reflex is elicited more easily than the latter and results in the greater contraction

Certain of the reflexes described by Barrington have been demonstrated experimentally in the dog by Dennig (1924) In experiments in which contraction of the bladder was elicited by means of water in the urethra, contraction of the detrusor muscle always took place at the instant when the pressure in the urethra became sufficient to open the external sphincter, regardless of the direction of the flow of the liquid The mere flowing of liquid through the distal part of the urethra did not elicit contraction of the bladder He therefore concluded that opening of the external sphincter constitutes the adequate stimulus for the micturition reflex

Dennig also demonstrated experimentally that voluntary micturition can be carried out following section of the pudendal nerves Although closure of the sphincter mechanism is less perfect following bilateral section of the pudendal nerve than before dogs which had previously been trained to micturate at a designated place persisted in this habit after section of the pudendal nerves, and discharged urine voluntarily whenever they were brought to the place in question Since no other somatic efferent fibers reach the bladder or urethra and the direct stimulating effect on the bladder of increased intra-abdominal pressure due to contraction of the abdominal muscles was ruled out due to the ease with which the flow of urine was brought about, Dennig concluded that voluntary impulses affect the bladder directly through the autonomic nerves Further experimentation also proved that the autonomic nerves involved are the parasympathetic and not the sympathetic nerves supplying the bladder Following section of the pudendal nerves section of the hypogastric nerves had no apparent effect on voluntary micturition Micturition could not be carried out voluntarily following section of the pelvic nerves leaving only the hypogastric nerves intact, until the bladder became adjusted so that it would contract in response to increased intra-abdominal pressure due to contraction of the abdominal muscles

In addition to showing that voluntary micturition can be carried out in the absence of functional pudendal nerves *i e* through the autonomic (parasympathetic) innervation of the bladder, Dennig's experimental results also shed some light on the specific functional defects of the bladder due to elimination of any one of the several components of its nerve supply Section of the pudendal nerves results in imperfect closure of the sphincter and loss of urethral sensibility, but does not materially disturb the normal functioning of the bladder otherwise Section of the hypogastric nerves

either alone or in addition to the pudendal nerves results in no marked changes in bladder function Section of the pelvic nerves brings about profound functional and trophic disturbances of the bladder Section of all the nerves to the bladder is followed by more or less constant flow of urine in small quantities but also periodic discharges of larger quantities brought about by mechanical stimuli to which the bladder is now hypersensitive Incomplete emptying and cystitis are common under these conditions

The time of onset and the efficiency of automatic micturition in cats following bilateral section of the pelvic nerves, according to Langworthy and Hesser (1936), are related to the development of rhythmic contraction waves in the bladder musculature and lowering of the intravesical pressure as liquid flows out through the urethra Following the onset of periodic micturition, the volume of the bladder drops below the normal level

Inasmuch as voluntary micturition can be carried out following section of the pudendal nerves, certain investigators have maintained that the autonomic mechanisms employed in micturition are subject to direct voluntary influences There is no evidence that contraction of the detrusor muscle can be initiated or continued by direct voluntary effort On the other hand, micturition cannot be adequately explained on the assumption that the posterior urethra and external sphincter constitute the only trigger zone for starting the act On the basis of all the data available including clinical and experimental observations on man, Learmonth (1931) has advanced the opinion that the bladder musculature and the internal sphincter also constitutes a "trigger zone for the initiation of the act of micturition When the bladder is adequately distended the opening of the internal sphincter is arranged for automatically This according to Learmonth "is the mechanism of micturition on desire to urinate" On the other hand voluntary relaxation of the internal sphincter is accompanied by automatic contraction of the detrusor muscle This, according to Learmonth, 'is the mechanism of voluntary micturition"

According to Denny-Brown and Robertson (1933), powerful contractions of the detrusor muscle which have a very short latent period and do not differ in form and rhythm from the spontaneous contractions of this muscle can be called forth by voluntary effort These contractions appear to be inseparably associated with relaxation of the musculature of the perineum Voluntary restraint of micturition exerts an inhibiting effect on the contractions of the detrusor muscle and is accompanied by contraction of the perineal musculature and closure of the external sphincter Since micturition may be initiated by voluntary effort and is subject to voluntary interruption at any point in the cycle it can hardly be regarded as purely reflex It may be urged that voluntary closure of the external vesical sphincter presents an insuperable barrier to the outflow of urine This however, is not an adequate explanation of the sudden interruption of the flow of urine particularly in the female since in the female the external sphincter is so feebly developed that it probably may be disregarded in considering the normal physiology of the bladder Sudden interruption of the outflow of urine, furthermore, is not followed by a feeling as if the detrusor muscle were contracting against a force which it is unable to overcome The available evidence favors the assumption that contraction of the detrusor muscle ceases simultaneously with the closure

of the internal sphincter and at once becomes tonically adjusted to the vesical content at the time. Clinical observations also indicate that the flow of urine may be voluntarily interrupted with a similar lack of discomfort following surgical destruction of the internal sphincter. In view of these facts, it must be assumed that the change in the behavior of the detrusor muscle is brought about reflexly by afferent impulses arising either in the internal or external sphincter or the impulses which interrupt the process of micturition are integrated at higher levels and both the detrusor muscle and the sphincters receive impulses simultaneously from these levels. The latter hypothesis obviously is the more attractive. According to Denny-Brown and Robertson (1933) the voluntary control of micturition is "effected solely by variation in voluntary and unconscious inhibition of the mechanism of spontaneous reaction to distention." If any hypothesis of this kind be accepted the concept of micturition as a purely reflex reaction must be limited to infancy. Voluntary control of micturition undoubtedly is facilitated by a normal functional balance of the sympathetic and parasympathetic nerves. True enuresis, according to Blyer (1938), probably involves hyperirritability of the parasympathetic innervation of the bladder.

Reflex micturition is mediated through centers located in the sacral segments of the spinal cord. The reflex centers for inhibition of the detrusor muscle and contraction of the internal vesical sphincter are located in the first and second lumbar segments of the spinal cord. These centers receive impulses through afferent nerves from other parts of the body as well as from the urinary bladder and its outlet including the sphincter mechanisms; consequently micturition may be facilitated or inhibited by stimuli effective in widely separated areas. Reflex responses of the bladder are elicited with greater facility by stimulation in certain areas than in others. Head and Riddoch (1917) described automatic emptying of the bladder in patients with extensive spinal lesions, as part of a "mass reflex" which could be evoked by stimulation of the lower extremities or other parts below the level of the lesion. Holmes (1933) has taken exception to this interpretation and has pointed out that the involuntary micturition which not infrequently is associated with spasms of the lower extremities in patients with spinal cord lesions is not the direct result of stimulation of the lower extremities but is due to the associated spasm of the abdominal wall which, by increasing the intra-abdominal pressure, suddenly increases the tension on the bladder musculature. According to his observations on patients with transverse lesions of the spinal cord the contractions of the bladder did not occur simultaneously with the spasm of the abdominal wall but after an interval, suggesting that the overflow of impulses into the micturition center did not take place immediately. The more vigorous contraction which expelled the contents of the bladder usually was preceded by a short series of oscillations of pressure. In patients in whom the site of the spinal cord lesion was so low that the reflex excited in the lower extremities did not spread to the abdominal muscles, spasm of the extremities was not accompanied by evacuation of the bladder. Langworthy (1939) described a "mass reflex" associated with voluntary micturition following spinal cord injury. After reflex micturition became established, in the case reported, impending micturition was accompanied by widespread involuntary movements of the lower extremities including the

toes The muscular contractions were associated with cramp-like pains in the contracting muscles and the urethra Micturition could be induced by stimulation of the perineal region but was delayed by holding the toes in extension Schlesinger (1933) emphasized the importance of stimulating the anterior abdominal wall by percussion or rubbing in order to elicit reflex contraction of the detrusor muscle in patients without spinal cord lesions in whom complete evacuation of the bladder is difficult If the first reflex response does not result in completely emptying the bladder, the reflex may be elicited a second and a third time after short intervening intervals

A frank lesion of the brain or spinal cord may result in complete vesical paralysis Retention of urine, in such cases usually is accompanied by overflow incontinence If the lesion is located above the lumbar segments of the spinal cord, cutaneous stimulation, particularly in the anterior abdominal area, may elicit reflex micturition If the paralysis is associated with a complete transverse lesion of the spinal cord, periodic emptying of the bladder may gradually become automatic after several weeks, unless complications, such as cystitis or pyelitis, have set in

In cases in which a spinal cord lesion causes acute paralysis of the bladder but leaves the sympathetic pathways intact and does not completely destroy the parasympathetic pathways a condition may develop following the acute phase, which is known as "cord bladder" Urinary retention is not complete in this condition and is not accompanied by incontinence Section of the hypogastric nerve, in such cases, may be followed by increased tonus of the detrusor muscle and reduction in the residual urine (Learmonth 1930) Parasympathetic stimulation also may be beneficial

The "atonic bladder' of childhood, which not uncommonly is associated with malformation of the sacral portion of the spinal cord usually exhibits an atonic detrusor muscle without dilatation of the sphincter, due to defective parasympathetic innervation, which renders establishment of a proper functional balance between the sympathetic and parasympathetic nerves impossible Bucy *et al* (1937) reported such a case in which section of the hypogastric nerves was followed by marked improvement in bladder function which had been maintained for three years Relaxation of the sphincter was regarded as the important factor in the improvement in bladder function in this case

Bladder Sensibility—Although the internal sphincter is composed of smooth muscle, it probably receives its afferent innervation at least in part through the pudendal nerves As stated above Learmonth (1931) regarded relaxation of the internal sphincter and the accompanying contraction of the detrusor muscle as the mechanism of voluntary micturition Experimental and clinical evidence suggests that both contraction of the detrusor muscle and relaxation of the internal sphincter play a part in the urge to voluntary micturition The sensations involved are not all of the same quality Indefinite sensations referred to the region of the bladder but not definitely localized probably result from impulses arising in the bladder musculature while the more acute sensations which can be more or less definitely localized at the neck of the bladder are brought about by afferent impulses arising in that region (Muller, 1924) By virtue of the physiologic character of the parasympathetic fibers distributed to the internal sphincter muscle, contraction of the detrusor also tends to bring

about reflex relaxation of the internal sphincter Under these conditions emptying of the bladder can only be prevented by voluntary contraction of the external sphincter If the external sphincter holds a short period of rest usually ensues during which the detrusor muscle relaxes somewhat and relieves the intravesical pressure If the bladder is not voluntarily emptied stronger contractions of the detrusor muscle set in and, if they succeed in pressing a few drops of urine into the urethra the impulse to micturate becomes irresistible and reflex micturition takes place If the external sphincter mechanism withstands the pressure produced by repeated contractions of the detrusor muscle this muscle may become inactive so that soon after the urge to micturate was at its maximum strength spontaneous micturition becomes impossible

According to Schwartz (1920) voluntary micturition is preceded by a sudden increase in intravesical pressure He regarded this as the cause of the emptying reflex Muller (1924) regarded it as the beginning of the emptying process He pointed out that increased intravesical pressure alone does not give rise to a flow of urine under physiologic conditions but that the primary cause of micturition is distention of the bladder wall According to Denny-Brown and Robertson (1933) the bladder reacts to distention by contraction of its musculature This is an adaptive process which does not intrude upon consciousness until the intravesical pressure reaches a certain level and the active vesical contractions reach a threshold intensity beyond which they give rise to sensations Passive distention of the organ also gives rise to sensation It is apparent therefore that sensation is only indirectly related to intravesical pressure since even slight enlargement of the organ may lower the threshold at which added spontaneous active contractions can produce sensation

According to Frohlich and Meyer (1922) electrical stimulation of the fundus of the bladder gives rise to afferent impulses mediated through the pelvic nerves which result in painful sensations Similar stimulation in the region of the sphincter gives rise to afferent impulses mediated through the pudendal nerve which also result in painful sensations These results afford definite information regarding the afferent pathways of impulses arising in circumscribed areas of the bladder but afford no unmistakable clues regarding the pathways of afferent impulses which result in the desire to micturate

In Dennig s experiments, marked distention of the bladder by filling it through a catheter resulted in uneasiness on the part of the animal If the distention elicited reflex contraction of the bladder musculature the animal exhibited increased uneasiness until the liquid began to escape along the catheter and the internal pressure was reduced Section of the pudendal nerves had no apparent effect on the uneasiness manifested by the animal due to artificial distention of the bladder When both hypogastric and pelvic nerves were cut, leaving the pudendal nerves intact the uneasiness manifested by the animal was much less marked Following section of all the nerves to the bladder the animal no longer manifested uneasiness regardless of the extent to which the bladder was artificially distended, therefore it may be assumed that either the pelvic or the hypogastric nerves play the major role in the conduction of afferent impulses which result in the urge to voluntary micturition This function probably is subserved mainly by the pelvic nerves, but clinical observations indicate

CHAPTER XIV

INNERVATION OF THE SEX ORGANS

THE MALE SEX ORGANS

Anatomic Data —Extrinsic Nerves — The testis receives its innervation through the spermatic plexus which also constitutes the major portion of the nerve supply of the spermatic cord The spermatic plexus is derived mainly from the aortic plexus but also receives fibers from the renal plexus It invests the spermatic artery throughout its course and communicates with the hypogastric plexus in the lower part of the ductus deferens The preganglionic and visceral afferent fibers involved in the sympathetic innervation of the testis in man are components of the tenth and higher thoracic nerves Some of the afferent fibers, according to Mitchel (1938), enter the spinal cord as high as the sixth thoracic segment The afferent fibers supplying the epididymis reach the spinal cord mainly through the eleventh and twelfth thoracic and first lumbar nerves In the cat and rabbit, according to Langley and Anderson (1895), the preganglionic and visceral afferent fibers involved in the sympathetic innervation of the sex organs are components of the second to the sixth lumbar nerves

The nerve supply to the seminal vesicle and ductus deferens is derived from the hypogastric plexus This plexus gives rise to a subordinate plexus which supplies the seminal vesicle and continues along the ductus deferens as far as the epididymis The epididymis receives fibers from both the hypogastric and the spermatic plexus

The prostatic plexus is a relatively large plexiform structure lying on either side of the prostate gland It includes both sympathetic and parasympathetic components The former are derived from the hypogastric plexus, the latter from the sacral parasympathetic outflow In addition to supplying the prostate and the prostatic urethra the prostatic plexus gives rise to the cavernous plexus of the penis The latter plexus gives rise to nerves which supply the corpora cavernosa penis and, communicating with branches of the pudendal nerves, sends rami to the corpus cavernosum urethræ and the penile portion of the urethra The retractor muscle of the penis, which occurs in many mammals, derives its nerve supply from the same sources as the smooth muscle of the urethra (Langley and Anderson 1895)

The glans and skin of the penis are supplied exclusively through branches of the dorsal nerve of the penis which arises from the pudendal nerve and consists of fibers derived from the third and fourth sacral nerves The compressor urethræ and ischiocavernosus and bulbocavernosus muscles, *i e*, the voluntary muscles employed in the act of ejaculation, also are innervated through branches of the pudendal nerve Vasoconstrictor fibers derived from the hypogastric plexus join the pudendal nerve to be distributed through its branches to the blood vessels of the penis

Intrinsic Nerves —The spermatic plexus is made up mainly of unmyelinated nerve fibers but includes some myelinated ones In the spermatic cord, it gives rise to numerous slender fiber bundles which are more or less

closely associated with the blood vessels Slender filaments derived from the spermatic plexus become associated with the ductus deferens and join the plexus on this duct Farther distalward nerve fibers become associated with the ductus epididymidis and supply the thin layer of smooth

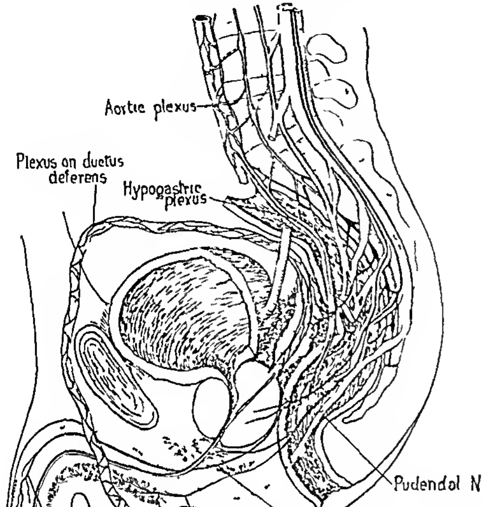


FIG 66 —Schematic illustration of the innervation of the male sex organs Dotted line indicates afferent cerebrospinal fibers double lines indicate sympathetic nerves heavy black lines indicate parasympathetic nerves

muscle in the wall of this duct Slender rami also occur among the ductuli efferentes Most of these are closely associated with blood vessels but also supply fibers to the very thin layer of smooth muscle in the walls of these ducts (Kuntz 1919)

The distribution of nerve fibers in the testis has been described by many investigators. Letzerich (1868) claimed to have traced fibers from nerves lying in the connective tissue between the seminiferous tubules through the membrana propria to their terminations on cells in the deeper layers of the seminal epithelium. Retzius (1893) could not substantiate this finding. Timofeew (1891), who studied the distribution of nerve fibers in the spermatic cord and testis in various mammals (rabbit, guinea pig, rat, cat, dog), described a rich plexus associated with the blood vessels, ductus deferens and ductus epididymidis. He also observed nerve fibers in proximity to the seminiferous tubules but found none which penetrate the membrana propria. He regarded the nerve fibers on the surface of the seminiferous tubules as fibers which supply small blood vessels. Cavalie (1902) described a rich plexus of nerve fibers associated with the blood vessels and seminiferous tubules in preparations of the testis of the fowl and rabbit and described terminal arborizations of these fibers among the cells in the deepest layers of the seminal epithelium and, in the rabbit, about the epithelial cells in the ductus epididymidis. Loisel (1902) also described nerve fiber terminations on both spermatogenic and sustentacular cells in the deep layers of the seminal epithelium.

In a study of the innervation of the testis of the dog by the use of the pyridine-silver method, Kuntz (1919) found nerve-fiber bundles in proximity to the vessels in the mediastinum testis and in the connective tissue between the seminiferous tubules but none which penetrate the membrana propria. An exhaustive search also failed to reveal any nerve fibers which terminate in relation to the interstitial secretory cells. The general distribution of nerve fibers in the testis seems to be determined by the distribution of the arteries and veins. Areas of connective tissue between the seminiferous tubules which contain no blood vessels except capillaries contain very few nerve fibers. These undoubtedly are associated with the capillaries. Pines and Maiman (1927) also failed to find nerve-fiber terminations in the seminal epithelium. They described end knobs in contact with the walls of the seminiferous tubules but obtained no evidence that nerve fibers penetrate the membrana propria. They also described terminations of unmyelinated fibers among the interstitial secretory cells which they regarded as the terminations of secretory fibers, and end bulbs in the connective tissue but not in relation to the blood vessels which they regarded as sensory in function. Okkels and Sand (1941) found the human testis more abundantly innervated than previous studies indicate. According to their report, the interstitial secretory cells are abundantly innervated through *fibers which effect direct contacts with the secretory cells*.

In view of the numerous negative findings and the available physiological data, direct innervation of the seminal epithelium and the interstitial secretory tissue must be regarded as extremely doubtful in spite of the few positive findings to the contrary.

The tunica albuginea and the tunica vasculosa are abundantly innervated. Numerous nerve fiber bundles are intimately associated with the blood vessels, others show no apparent relation to the blood vessels. Many components of the latter and some of the former undoubtedly are afferent.

The prostatic plexus, the plexus on the seminal vesicle and the cavernous plexus of the penis include sympathetic, parasympathetic and afferent components. In the fatty connective tissue between the prostate gland

and the seminal vesicle occur numerous very small flattened ganglia some of which are incorporated in the prostatic plexus others in the plexus on the seminal vesicle Nerve fibers may be traced from these plexuses into the prostate gland and the seminal vesicle Small ganglia also occur in the cavernous plexus of the penis None have been found in the plexus on the ductus deferens The neurons in the small ganglia in these plexuses are relatively small and exhibit numerous short dendrites which in general terminate within the cell capsule In this respect they differ from the majority of the neurons in the ganglia of the sympathetic trunk Muller and Dahl (1912) were inclined to regard them as neurons of a distinct type, although the ganglia of the sympathetic trunk also contain some neurons whose dendrites do not penetrate the cell capsule Inasmuch as some of the dendrites of neurons in these small ganglia penetrate the cell capsule, there seems to be no adequate reason to regard them as a distinct morphologic type They probably fall within the range of normal morphologic variation of autonomic neurons No ganglion cells have been found within the prostate gland or the seminal vesicle Both are penetrated by unmyelinated and myelinated nerve fibers but the terminations of these fibers have not been described

The nerves which arise from the cavernous plexus of the penis contain relatively few myelinated fibers In addition to supplying the membranous and penile portion of the urethra they also supply the blood vessels and smooth muscle of the corpora cavernosa penis the corpus cavernosum urethrae and the skin of the penis

Sense organs in the glans penis have been described by numerous investigators They occur in considerable abundance in both the superficial and deeper layers of the chorium They have been variously regarded as similar to Pacinian corpuscles, end bulbs of Krause and sense organs which are characteristic for the external genital organs While they exhibit a wide range of variation in various mammals they probably do not differ in any essential respects from the cutaneous sense organs found in other parts of the body They are connected with the terminal branches of afferent fibers which are incorporated in the dorsal nerve of the penis and reach the spinal cord through the pudendal nerve

Physiologic Data —Effects of Sympathetic and Parasympathetic Stimulation —Our knowledge of the role of nerve impulses in the regulatory control of the functions of the male sex organs is based mainly on the findings of early physiologists Recent investigations have added much to our knowledge of the general physiology of the male reproductive system but little that bears directly on the role of nervous regulation in the functioning of this system

Budge (1858) observed that electrical stimulation of the communicating rami of the third and fourth lumbar nerves in the rabbit elicits contractions of the ductus deferens which are propagated from the testis toward the seminal vesicle Stimulation of the inferior mesenteric ganglion or the hypogastric nerves elicits the same reaction of the ductus deferens but stimulation of the aortic plexus above the inferior mesenteric ganglion calls forth no reaction of the ductus deferens These findings established the important fact that the spinal center through which motor activities of the ductus deferens and seminal vesicle are mediated is located in the lumbar segments of the spinal cord

Eckhardt (1863) found that electrical stimulation of the visceral rami of the sacral nerves in the dog elicits erection of the penis He, therefore designated these rami the 'nervi erigentes' He could elicit no reaction of the penis by electrical stimulation of the pudendal nerve but observed that mechanical stimulation of the glans no longer results in erection of the penis following section of the pudendal nerve He also failed to bring about erection by painful stimulation of the central end of the severed pudendal nerve These findings established the important role of the pelvic nerves in the process of erection and suggested the rôle of the afferent pudendal fibers in erection elicited by stimulation of the glans

Nikolsky (1879) observed that section of the nervi erigentes is followed by contraction of the blood vessels in the penis and that electrical stimulation of the peripheral ends of these nerves elicits dilatation of the blood vessels and filling of the sinuses in the erectile tissue Frank (1895) also observed vasodilatation of the penis in response to stimulation of the nervi erigentes He also determined experimentally that the fibers which join the pudendal nerve from the hypogastric plexus exert a constrictor effect on the blood vessels of the penis

Mislawsky and Bormann (1898) observed that in addition to their motor effect on the musculature of the ducti deferentia and seminal vesicles the hypogastric nerves also exert a true secretory influence on the prostate gland Certain experimental data reported by Mislawsky (1927) indicate that the prostate receives both secretory and inhibitory fibers In man according to Learmonth (1931) stimulation of the sympathetic nerves in the pelvis results in the expulsion of semen from the ejaculatory ducts, due to contraction of the musculature of the seminal vesicles and expulsion of secretion from the prostatic ducts due to contraction of the smooth muscle which permeates the prostate gland

According to Langley and Anderson (1895), stimulation of the lumbar communicating rami or the lower lumbar sympathetic trunk in animals (rabbit cat dog) results in constriction of the blood vessels in the penis as well as contraction of the retractor penis muscle On the basis of their experimental results they concluded that the preganglionic fibers involved in vasoconstriction in the external genitalia are components of the upper lumbar nerves They found no satisfactory evidence that the lumbar nerves contain vasodilator or inhibitory fibers for the external genitalia Following section of the lumbar nerves or extirpation of the lower lumbar portion of the sympathetic trunks, mild erection may come about due to the removal of the vasoconstrictor influence of the hypogastric nerves Langley and Anderson like various other investigators, also confirmed the finding of Budge that stimulation of the lumbar nerves elicits contraction of the entire musculature of the ducti deferentia and seminal vesicles

Spina (1897) observed erection and ejaculation in the absence of stimulation of the genitalia in a guinea-pig following transection of the spinal cord in the lower thoracic region He also observed that if the spinal cord is destroyed in a guinea pig by passing a slender rod downward through the vertebral canal, ejaculation without erection is elicited when the end of the rod reaches the lumbar region

Muller (1901) reported the results of experiments in which dogs which had been subjected to extirpation of the lower lumbar and sacral portions of the spinal cord, in spite of the paralysis of the posterior portions of the

body, exhibited erection in response to appropriate stimulation Pressure on the abdomen which resulted in emptying of the bladder in these dogs, also resulted in reflex erection of the penis Likewise reflex erection could be elicited by direct stimulation of the glans or shaft of the penis but none of these stimuli elicited ejaculation

Although the genital organs normally are subject to regulatory influences through the autonomic nerves sympathetic denervation of these organs has no marked effect on their functional activity except in the prevention of ejaculation due to paralysis of the smooth muscle of the seminal vesicals and the ejaculatory ducts According to Bacq and Brouha (1932) sympathetic denervation of the genital organs in male rats, guinea-pigs and rabbits has no influence on puberty or the internal and external secretory activity of the testes These organs also remain sensitive to the anterior pituitary hormone The changes which take place in the genital tract, particularly the seminal vesicles according to Bacq and Brouha are more marked following extirpation of the hypogastric ganglia than following extirpation of the abdominal sympathetic trunks

In experiments reported by Farrell and Lyman (1937) stimulation of the hypogastric nerves in the dog resulted in increased secretory activity of the prostate gland and wave-like contractions of its capsule Stimulation of the pelvic nerves resulted in marked contraction of the musculature in the stroma of the prostate but caused no increase in the secretory activity of the gland Administration of adrenin pilocarpine nicotine or acetylcholine resulted in increased prostatic secretory activity On the basis of these findings they concluded that the secretory fibers to the prostate are cholinergic components of the sympathetic nerves

Reflex Regulation Through Centers in the Spinal Cord —The results of animal experimentation cited above clearly indicate that reflex erection is mediated through centers in the lumbar and sacral segments of the spinal cord and another in the lumbar spinal cord which mediates reflex ejaculation There is no conclusive evidence that either the erection or the ejaculation reflex can be carried out through the plexuses associated with the genital organs alone either in the intact animal or following destruction of the centers in question Erection may be brought about by psychic stimulation following destruction of the sacral spinal cord but not following destruction of the lumbar cord It must be assumed therefore that the efferent impulses involved in bringing about erection due to psychic stimulation, in the absence of the sacral center, are mediated through the lumbar center and the vasomotor nerves to the cavernous bodies

In view of all the data available, the existence of a sacral center which mediates erection and a lumbar center which mediates ejaculation may be regarded as established The lumbar center under certain conditions apparently may mediate erection but ejaculation cannot be mediated through the sacral center Reflex erection and ejaculation can only be carried out through these centers

Erection —The act of erection involves engorgement of the cavernous bodies in the penis, particularly the corpora cavernosa In mammals which do not possess a long os penis according to Deysach (1939), the venæ profundæ in the cavernous bodies possess thick muscular walls similar to those of arteries Most of the numerous side branches of these veins have very thin walls which extend through all the layers of the thick

wall of the vein (small sluice channels) The others exhibit the typical histological structure of veins in other tissues (large sluice channels) When the arteries which supply the erectile tissue dilate, thus permitting more blood to flow into the cavernous bodies, a mild state of erection is produced which may be called "arterial erection" Compression of the veins which drain the cavernous bodies also results in a mild state of erection which may be called "venous erection" Erection of either of these types may be adequate for copulation in mammals which possess a long os penis Erection which is adequate for copulation in mammals devoid of a long os penis requires closure of the sluice valves which consist of the thick walls of the venae profundae and the small sluice channels The reactions of these vessels are determined in part by nerve impulses and in part by mechanical factors

Erection may be brought about as a purely reflex reaction or as a result of psychic stimulation It is mediated mainly through the parasympathetic nerves The normal innervation of the cavernous tissue particularly that of the vascular musculature includes sympathetic nerve fibers The latter are not essential for engorgement of the cavernous bodies since erection may take place following sympathetic denervation of the penis Sympathetic stimulation generally tends to inhibit erection due to limitation of the volume of blood which may flow into the cavernous bodies by constriction of the arterioles Dilatation of the arterioles coincides with inhibition of the smooth muscle in the walls of the venous sinuses and partial closure of their outlets through the small sluice channels This partial closure undoubtedly involves mechanical factors brought into play by the rapid rise in pressure within the cavernous bodies According to Henderson and Roepke (1933), erection does not involve compression of the efferent veins by the action of skeletal muscles but the ischiocavernosus and bulbocavernosus muscles undoubtedly play a role in this reaction Removal of the ischiocavernosus and bulbocavernosus muscles in dogs, in experiments reported by Lowsley and Bray (1936), resulted in inability to perform effective copulation Shortening of these muscles by plication on the contrary, resulted in increased sexual activity Excessive shortening resulted in priapism They also reported relief of impotence in man in certain cases, following plication of these muscles

Under normal conditions engorgement of the cavernous tissue subsides as soon as the stimulation which caused it ceases If ejaculation takes place, erection commonly subsides promptly since the stimulus which elicits contraction of the seminal vesicles and the ejaculatory ducts also elicits constriction of the arterioles in the cavernous tissue, thus relieving the turgor Since all the smooth muscle in the penis reacts in the same manner the organ may be reduced temporarily to less than its normal size In animals in which the penis is provided with a retractor muscle, the reflex reactions associated with ejaculation include contraction of this muscle, resulting in retraction of the organ In experiments on cats reported by Oppenheimer (1938), the retractor penis muscle contracted in response to either sympathetic or parasympathetic stimulation

Contraction of all the smooth muscle in the penis may be associated with psychic states which counteract sexual desire e g , disgust or fear, or by cold applications to the skin of the organ or adjacent areas, including the upper portions of the thighs Temporary contraction of the penis not

uncommonly occurs during a cold bath Mild engorgement of the erectile tissue may be elicited by warm applications or by a warm bath

The duration of erection associated with sexual excitation is determined in part by the reactivity of the reflex mechanisms employed and in part by psychogenic factors Prolonged, continuous erection (priapism) must be regarded as pathologic This condition not uncommonly is associated with local irritation injury to the cavernous tissue leukemia or a lesion of the spinal cord In certain cases it is psychogenic

In the absence of anatomical barriers which prevent the normal outflow of the blood from the cavernous bodies maintained engorgement may be due to excessive parasympathetic stimulation The clinical observation of Paas (1934) that extensive bilateral lumbosacral sympathectomy failed to relieve persistent priapism seems to support this assumption Resection of the cavernous plexus undoubtedly would relieve priapism of neurogenic origin but it would also result in impotence Therapeutic measures designed to depress the parasympathetic reflex mechanisms and appropriate psychotherapy obviously are indicated in the treatment of priapism

Impotence of neurogenic origin may be psychogenic or due to sympathetic hyperreactivity or hyporeactivity of the reflex mechanisms employed in the act of erection In cases which fall within the first category appropriate psychotherapy is indicated The inhibitory effect of sympathetic stimulation on erection is evidenced by the fact that emotional states characterized by strong sympathetic excitation and the administration of adrenin tend to inhibit this reaction In cases of functional virile impotence, as reported by Pende (1937) bilateral lumbar sympathectomy was followed by marked improvement in erections although the ability to ejaculate was lost The spinal center through which inhibition of erection is mediated according to Deakin (1938) is located at a lower level than the ejaculatory center He reported erection with ejaculation in dogs following bilateral section of the lower lumbar sympathetic nerves In view of these findings it seems not improbable that in man the nerves through which erection is inhibited could be interrupted without damage to the ejaculatory mechanism In cases of impotence due to hyporeactivity of the reflex mechanisms employed in erection parasympathetic stimulation is indicated

Ejaculation —Ejaculation is not a necessary accompaniment of erection In normal healthy individuals in the waking state the discharge of seminal fluid normally is elicited only by stimulation of the glans This reaction in a large measure depends on the quality of the stimulus Simple contact, electrical or thermal stimulation or pain usually *do* not elicit *ejaculation* The adequate stimulus seems to be gentle friction particularly of the moist glans The necessary duration of such stimulation depends on conditions affecting the individual such as his general physical condition age, psychic excitability and the secretory content of the sex glands

Ejaculation is essentially a reflex reaction Afferent impulses arising in the sense organs in the glans are conducted to the spinal cord through components of the pudendal nerves The efferent impulses involved arise in the upper lumbar segments of the spinal cord and traverse the lumbar communicating rami and the hypogastric nerves Ejaculation cannot be elicited following extirpation or destruction of the lumbar spinal cord or section of the sympathetic nerves to the pelvic organs

Inasmuch as stimulation of the glans, under normal conditions, must be continued at least for a short interval in order to elicit ejaculation, this reaction must involve the summation of impulses, which probably occurs in the ejaculatory center in the lumbar spinal cord When such summation has reached the threshold level, a sudden discharge of efferent impulses takes place which calls forth sudden contraction of the smooth musculature of the entire internal sexual apparatus resulting in the propulsion of seminal fluid into the urethra This in turn elicits reflex contraction of the striated constrictor urethrae, bulbocavernosus and ischiocavernosus muscles which brings about the expulsion of the seminal fluid from the urethra The ejaculatory act consequently is completed by the reflex contraction of voluntary muscles Premature ejaculation is commonly associated with hyperirritability of the reflex mechanisms employed, delayed ejaculation with hypoirritability of these mechanisms In certain cases either premature or delayed ejaculation may be psychogenic

The discharge of seminal fluid may take place during sleep (nocturnal emission) in the absence of specific stimulation of the glans The adequate stimulus involved in nocturnal emission is unknown It has been generally assumed that erotic dreams constitute an important factor in this reaction Similar psychic manifestations during the waking state at least in healthy individuals, however, do not call forth the discharge of seminal fluid It may be assumed that certain inhibitory influences which prevent this reaction to psychic stimulation during the waking state are not effective during sleep On the other hand erotic dreams in some instances probably are a consequence rather than the cause of nocturnal emissions That the discharge of seminal fluid during sleep as well as during the waking state gives rise to afferent impulses which result in psychic manifestations is certain Possibly, erotic dreams associated with nocturnal emissions are to be regarded only as the outcome of such psychic manifestations It seems highly probable that the discharge of seminal fluid may be called forth reflexly during sleep by the stimulus afforded by internal pressure particularly in the seminal vesicles and prostate gland, due to the accumulation of seminal and prostatic secretion The data available at present do not afford an adequate basis for the complete understanding of this sexual phenomenon

The Sexual Orgasm —The sensations immediately associated with ejaculation constitute the sexual orgasm They arise simultaneously with the initiation of the peristaltic contraction of the ducti deferentia The beginning of the orgasm, consequently, precedes the expulsion of the seminal fluid from the urethra by a short interval

How and where the sensations which constitute the sexual orgasm arise is not definitely known It has been assumed that the afferent impulses involved arise in the genital organs as a result of the contraction of the smooth musculature involved in the ejaculation reflex Learmonth (1931), however, has reported that male patients, following section of the sympathetic nerves to the pelvic organs, are still able to perform the sexual act and experience a psychic orgasm which is indistinguishable from the normal although ejaculation does not take place The afferent impulses involved probably are conducted into the spinal cord mainly by visceral afferent fibers and reach the appropriate integrating centers via the same ascending pathways which also conduct other visceral impulses which give rise to

sensations Inasmuch as sexual sensations are essentially of a primitive type it need not be assumed that all the afferent impulses which play a part in sexual feeling or awareness reach the cerebral cortex Many of them undoubtedly are integrated in the diencephalon

The impulses which give rise to the sexual orgasm also call forth reactions in other visceral organs The excitation apparently spreads throughout the entire autonomic nervous system Both the rate and force of the cardiac contractions are augmented respiration is stimulated and not uncommonly perspiration is called forth These impulses also give rise to somatic reflexes In addition to the contractions of the compressor urethræ ischiocavernosus and bulbocavernosus muscles which play a part in the expulsion of the seminal fluid spastic contractions of the extensor muscles of the lower extremities not uncommonly occur simultaneously with the orgasm According to Muller and Dahl (1912) the reflexes involved in these somatic reactions are carried out through reflex centers in the spinal cord They observed clonic contraction of the extensor muscles of the hind limbs simultaneously with the expulsion of seminal fluid elicited by artificial stimulation of the glans of the erect penis in a dog following transection of the spinal cord above the lumbar region

Cortical Influences — As pointed out above the data available do not justify the conclusion that either the seminal epithelium or the interstitial secretory tissue in the testis are innervated directly Psychic influences nevertheless play an important role in the control of the organs directly involved in the sexual act therefore it has been assumed by some that the sex organs are represented in the cerebral cortex This undoubtedly is true of the striated musculature involved but as pointed out above the discharge of seminal fluid cannot be called forth as a purely voluntary act There is no conclusive evidence therefore that the smooth musculature involved either in the process of erection or the act of ejaculation receives direct cortical impulses This musculature responds reflexly to a variety of stimuli arising within the organism as a result of sexual excitation and external stimulation of the penile organ particularly the glans

Sexual excitation is a complex phenomenon which in a large measure depends on the functional state of the internal secretory tissue in the sex glands It cannot be brought about during childhood until the sex glands particularly the internal secretory tissue have become functional If the sex glands are removed early the development of the seminal vesicles and prostate gland is arrested and sexual excitation never can be achieved On the other hand, overactivity of the internal secretory function of the sex glands results in a state of sexual hyperexcitability The *functional* balance between the sex glands and other endocrine organs plays an important role, consequently it may be assumed that the psychic functions of the cerebral cortex are influenced by the internal secretions of the sex glands and other endocrine glands and that sexual excitability, in a large measure, is determined by cortical reactions to these influences Sexual excitability and sexual desire, furthermore vary with the physiologic condition of the sex glands This is apparent particularly in those species which have a limited mating season In man voluntary inhibition also plays an important role in sexual excitability and under normal conditions, is the controlling factor in sexual behavior

THE FEMALE SEX ORGANS

Anatomic Data —Extrinsic Nerves—The ovary is innervated mainly through the ovarian plexus This plexus arises from the aortic and renal plexuses and accompanies the ovarian artery Many of the fiber bundles which enter the ovarian plexus may be traced directly from the ovarian ganglion located near the origin of the ovarian artery, and the ganglia incorporated in the renal plexus These ganglia are intimately connected

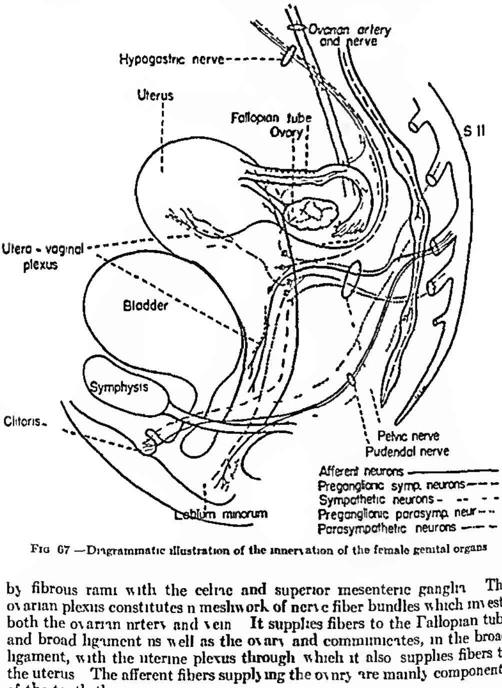


FIG 67 —Diagrammatic illustration of the innervation of the female genital organs

by fibrous rami with the celiac and superior mesenteric ganglia The ovarian plexus constitutes a meshwork of nerve fiber bundles which invests both the ovarian artery and vein It supplies fibers to the Fallopian tube and broad ligament as well as the ovary and communicates, in the broad ligament, with the uterine plexus through which it also supplies fibers to the uterus The afferent fibers supplying the ovary are mainly components of the tenth thoracic nerve

In addition to the fibers derived from the ovarian plexus the Fallopian tube also receives fibers from the intermesenteric nerves, the hypogastric

plexus and the uterine plexus The afferent fibers supplying the Fallopian tube reach the spinal cord through the eleventh and twelfth thoracic and lumbar nerves

The uterus is innervated mainly through the uterine plexus which is intimately connected with the vaginal plexus and, with the latter, constitutes the utero-vaginal plexus This plexus corresponds to the prostatic plexus in the male The utero-vaginal plexus is continuous superiorly with the hypogastric plexus but also receives fibers directly from the lower lumbar and sacral sympathetic trunk and the pelvic nerves, consequently, it includes both sympathetic and parasympathetic components It also includes a variable number of ganglia, one of which, the cervical ganglion,

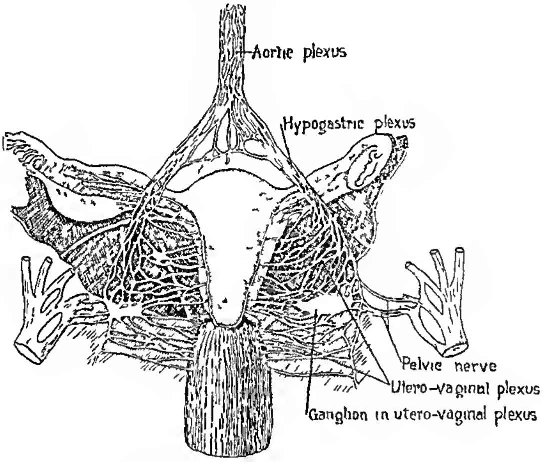


Fig 68 —Diagrammatic illustration of the extrinsic nerves of the uterus and vagina (After Dahl)

situated about the level of the cervix uteri usually is considerably larger than the rest and, in some instances includes most of the ganglion cells in the plexus As demonstrated by the use of paravertebral anesthesia afferent nerve fibers reach the uterus via the roots of the eleventh and twelfth thoracic nerves in the human species and via the first and second lumbar nerves in the dog (Cleland, 1933)

The vaginal plexus is made up mainly of parasympathetic components derived from the sacral parasympathetic outflow but also includes sympathetic components derived in part from the hypogastric plexus and in part directly from the sacral sympathetic trunk It supplies fibers to the wall and mucous membrane of the vagina and urethra and gives rise to a

cavernous plexus for the clitoris The latter structure also is supplied by the dorsal nerve of the clitoris which is a branch of the pudendal nerve

The labia are supplied by both cerebrospinal and autonomic nerves The cerebrospinal supply of the anterior part of each labium is derived from branches of the ilio inguinal, and that of the posterior part from branches of the pudendal nerve and the perineal branch of the posterior cutaneous nerve of the thigh The autonomic supply is derived from the vesical and vaginal plexuses

Intrinsic Nerves of the Ovary —Nearly all the nerve fibers which enter the ovary from the ovarian plexus are unmyelinated and of small caliber They accompany the ovarian vessels into the stroma where the larger bundles give rise to branches which accompany the branches of the ovarian vessels Nerve fibers are supplied to all the ovarian vessels and other smooth muscle in the ovary but not to the ovarian follicles and the interstitial secretory tissue

Among the early investigators Frankenhauser (1867) Waldeyer (1870) Elischer (1876), Riese (1891), von Herff (1892) von Gawronsky (1894) and Winterhalter (1896) described the intrinsic nerves of the ovary as supplying the ovarian follicles as well as the blood vessels Vedeler (1890) described an abundant nerve supply to the blood vessels in the human ovary but observed no fibers which enter the follicles Retzius (1893) de Vos (1894) and Mandl (1895) observed nerve fibers in proximity to the follicles but could not determine that they either penetrate the follicles or terminate in relation to them The occurrence of ganglion cells in the ovary was reported particularly by Bocura (1897) and Markowitin (1899) Abel and McIlroy (1912) observed no ganglion cells in the ovaries of the dog cat and rabbit According to their observations, the nerves, on entering the ovary at the hilum, become separated into three sets, a vascular, a follicular and an interstitial set all of which anastomose with one another They described the follicular nerves as lying in the tunicæ externa and interna but not as penetrating the stratum granulosum Brill (1915) described and illustrated a ganglion in the stroma of the ovary in the mouse and the rabbit, which he regarded as intimately associated with the nerve fiber bundles which enter the organ He also described an abundant supply of nerve fibers to the interstitial secretory tissue and traced structures which he regarded as nerve fibers into the corpus luteum to their terminations on lutein cells

In pyridine-silver preparations of ovaries of the dog, Kuntz (1919) observed an abundant nerve supply to the blood vessels and fibromuscular tissue in the stroma, but no nerve fibers which either penetrate the ovarian follicles or terminate in relation to them Near the periphery of the medulla and in the deeper layers of the cortex, many nerve fibers come into close proximity to aggregates of interstitial cells but careful observation failed to reveal any which terminate in relation to these cells In areas of the cortex in which the interstitial secretory tissue is best developed, nerve fibers are relatively rare They do not penetrate these areas except as they accompany blood vessels which either supply the interstitial tissue or pass through it In preparations of ovaries which contained well-developed corpora lutea a few nerve fibers in some instances, could be traced along the larger blood vessels in the connective tissue between the columns of lutein cells but none were observed to deviate from the blood vessels or to

assume a relationship to the lutein cells Ganglion cells were not observed within the ovary in any of the preparations studied

In experiments reported by Goecke and Beaufays (1936), nerve fibers in ovarian transplants soon underwent degeneration but new sympathetic fibers grew into the transplanted tissue from adjacent blood vessels Goecke (1938) traced nerve fibers into close proximity to follicles in the human ovary but not into them

Although not a few of the earlier investigators were led to conclude that nerve fibers actually penetrate the ovarian follicles and also supply the interstitial secretory tissue in the ovary we do not regard the evidence as convincing The available physiologic data also fail to support the conclusion that these tissues have a functional nerve supply The entire efferent nerve supply to the ovary probably is distributed solely to the blood vessels and other structures in the ovary which contain smooth muscle Ganglion cells undoubtedly have been observed within the ovary in certain cases but nerve cells do not occur regularly in this organ

Intrinsic Nerves of the Fallopian Tube —The Fallopian tube is innervated through both unmyelinated and myelinated fibers derived from the ovarian and uterine plexuses As the nerves penetrate the wall of the tube they give rise to branches which are distributed to all the layers except possibly the mucous epithelium A definite plexiform arrangement of these fiber bundles is not apparent

Among the early investigators who studied the innervation of the Fallopian tube von Herff (1892), Gawronski (1894) and others supported the theory that nerve fibers penetrate the mucous epithelium and terminate in relation to the epithelial cells They also claimed to have observed nerve cells in the wall of the tube Dahl (1916) described nerve fibers in all the layers of the Fallopian tube except the mucous epithelium He observed very fine branching fibers which approach the epithelium very closely but could not determine that they actually terminate in relation to the epithelial cells Harting (1929) described the nerve supply in the wall of the tube as abundant and pointed out that the fibers in the mucosa decrease in number toward the uterine end of the tube whereas those in the musculature increase He also reported the existence of bodies similar to tactile corpuscles in the mucosa in the upper third of the tube Neither Dahl nor Harting observed ganglion cells in the tube

The Utero-vaginal Plexus includes both myelinated and unmyelinated nerve fibers The cervical ganglion varies greatly in size and compactness If this ganglion is large and its component ganglion cells are compactly aggregated there are relatively few small ganglia scattered about in the plexus If the cervical ganglion is relatively small or comprises relatively few ganglion cells arranged in loosely aggregated groups there is a relatively large number of small ganglia scattered about in the plexus Blotevogel (1927) proposed the following classification of the ganglia cervicale uteri in the human and various animal species (1) Forma compacta This is a large compact ganglion which is traversed by all the nerves which join the uterus Cervical ganglia of this type occur in the mouse rat hyena and sometimes in the human species (2) Forma disseminata The ganglion complex does not exhibit a single large ganglion but a small ganglion occurs near the uterus in the course of every nerve joining this organ This arrangement is observed in the cat, kangaroo and, in some instances accord-

ing to various observers, in the human species (3) Forma compacta disseminata Cervical ganglia of this type consist of a large ganglionic mass made up of numerous groups of ganglion cells which are loosely associated with one another This arrangement occurs in the cat ape and, in some instances in the human species In all cases in which a large cervical ganglion exists, it is situated on the dorsolateral aspect of the uterus and in proximity to the upper end of the vagina Pemlschka (1929) reported that he never observed a large compact ganglion in the utero-vaginal plexus in the human species The neurons in the cervical ganglion and the smaller ganglia in the utero-vaginal plexus are similar morphologically to the ganglion cells in other parts of the autonomic nervous system

Intrinsic Nerves of the Uterus —Nerve fibers enter the wall of the uterus from the utero-vaginal plexus mainly along the blood vessels The larger trunks lie deep within the myometrium and approximately parallel to the long axis of the organ As observed by Brown and Hirsch (1941) in the immature human uterus, branches which extend into the endometrium form an intricate plexus in the lamina propria which is more abundant in the cervical canal than in the body of the uterus The nerves which supply the fundic area traverse the broad ligament or the superficial layer of the myometrium Within the myometrium, according to Dahl (1916) the smaller nerve fiber bundles in general run parallel to adjacent bundles of muscle fibers to which they give off branches the fibers of which terminate in relation to muscle cells He described the nerve supply as fairly uniform throughout the uterine wall except in the areas adjacent to the Fallopian tubes where it is particularly abundant

Nearly all the investigators who studied the intrinsic nerves of the uterus emphasized the abundance of nerve fibers in the musculature and along the blood vessels Certain of them traced nerve fibers into the uterine mucosa and claimed to have observed nerve fiber terminations in relation to the epithelium Others observed no nerve fibers which actually reach the mucous epithelium In view of the profound degenerative and regenerative changes which take place in the uterine mucosa, the existence of nerve fiber terminations in the epithelium must be regarded as extremely doubtful In preparations of the adult human uterus State and Hirsch (1941) observed nerves throughout the basal third of the endometrium According to their findings these nerves are related mainly to the arteries but some fibers end freely in the stroma Their data afford no evidence of fiber terminations in relation to the epithelium

Certain investigators described elements in the wall of the uterus in the human and animal species which they interpreted as ganglion cells others found no ganglion cells within the uterine wall According to Naditsch (1930) ganglion cells are present in the subserous layer in the region of the cervix but not in the deeper layers Okamura (1939) reported the occurrence of ganglion cells in the uterine wall in the cat and the rat According to his account, such cells are present in considerable abundance in the perimetrium and the myometrium and in small numbers along the nerves in the endometrium In spite of these positive findings, all the data available at present do not warrant the conclusion that ganglion cells occur regularly in the uterine wall

Intrinsic Nerves of the Vagina —Most of the nerves which join the vagina from the utero-vaginal plexus enter its upper and middle parts No nerves of macroscopic size can be traced from this plexus to the lower part of the vagina The intrinsic nerves of the vagina form a plexiform meshwork which includes numerous small ganglia

According to Gawronski (1894) some of the vaginal nerves extend through the muscularis into the mucosa and terminate in the vaginal epithelium Some of the early investigators also described end organs similar to Pacinian corpuscles in the vaginal mucosa

Jung (1905), Dahl (1916) and Medowar (1928) described a relatively simple plexiform arrangement of nerves which includes small ganglia in the upper and middle parts of the vaginal wall According to Dahl the neurons in these ganglia are morphologically identical with those in the utero-vaginal plexus He found no ganglion cells either in the lower part of the vagina or in the inner layers of the muscularis and the connective tissue between the muscularis and the vaginal epithelium and no receptive end organs in the vaginal mucosa

Nerves of the External Genitalia —Sensory end organs in the female external genitalia were observed by not a few of the early anatomists On the basis of their accounts and the results of his own histological studies, Dahl (1918) advanced the opinion that the various morphologic types of sensory end organs in the female external genitalia possess certain common characteristics Although they vary in form and structure the arrangement of the terminal portions of the nerve fibers with which they are connected is quite uniform He therefore proposed that they be regarded collectively as genital sense organs He found these organs present in abundance in the clitoris and labia minora but absent in the labia majora He also pointed out that they are less abundant but situated more superficially in the labia minora than in the clitoris In general the genital sense organs are separated from the surrounding tissue by connective-tissue capsules The afferent nerve fibers with which they are connected are myelinated components of the nerve of the clitoris and reach the spinal cord through the pudendal nerve

In addition to the myelinated fibers which terminate in the genital sense organs the external genitalia are supplied with unmyelinated nerve fibers Some of the latter lie close to the epidermis but most of them obviously are related to the blood vessels The unmyelinated nerve fibers in the clitoris and labia minora are derived mainly from the cavernous plexus of the clitoris

Physiologic Data —The early literature bearing on the role of the nervous system in the regulatory control of the female sex organs is exceedingly abundant and replete with conflicting data and conclusions which in the light of present knowledge obviously are erroneous A comprehensive review of this literature in this connection could serve no useful purpose, therefore an attempt will be made to state the main facts regarding the role of nervous influences in the functional control of the female sex organs with only such references to the literature as may be necessary to indicate the experimental background of the current physiologic concepts of the functional innervation of the female reproductive system

Functional Regulation of the Ovary —Although the ovary is abundantly supplied with nerve fibers the distribution of these fibers seems to be

limited to the blood vessels and the fibromuscular tissue in the stroma. There is no conclusive evidence for the direct functional innervation either of the ovarian follicles or the interstitial secretory tissue, therefore it cannot be assumed that the ovarian functions are subject to direct nervous regulation. They are influenced by vasomotor changes in the ovary which are mediated through the ovarian plexus and the nerves arising from it which innervate the ovarian blood vessels. Hinsey and Markee (1932) have reported ovulation, induced by the injection of pregnancy urine, in rabbits in the complete absence of functional nerve fibers to the ovary. Spontaneous ovulation also has been reported in totally sympathectomized animals.

Functional Regulation of the Fallopian Tubes, Uterus and Vagina.—The smooth musculature of the female genital tract has the capacity to undergo rhythmic contractions in the absence of nerve impulses. The activity of this musculature is regulated in part through hormonal agents and in part through its innervation. The importance of the non-nervous factors is emphasized by the records of spontaneous activity and the reported instances of parturition following partial or complete denervation of the genital organs.

Spontaneous contractions of the musculature of the Fallopian tubes, the uterus and the vagina have been recorded by many investigators. These records indicate that the musculature of the entire genital tract is capable of automatic activity in a high degree.

Hein (1902) reported spontaneous birth of rabbits at full term following section of all the nerves to the uterus. Cannon *et al.* (1930) reported spontaneous parturition in cats and dogs following complete extirpation of both sympathetic trunks. Parturition in the human species following sympathetic denervation of the genital tract also has been reported. In four cases reported by Bittmann (1938) in which the hypogastric nerves had been interrupted, parturition took place quite normally but probably somewhat more rapidly in all its phases than would have been the case with the sympathetic nerves intact. The labor pains also were reduced in intensity.

Spontaneous parturition following experimental denervation of the genital tract or following lesions of the spinal cord which result in paralysis of the lower half of the body commonly proceeds with abnormal rapidity. The contractions of the uterus seem to be more powerful than under normal innervation. Impulses normally emanating from the central nervous system undoubtedly exert an inhibitory influence in uterine activity (Zimmermann, 1914; Schmidt, 1915). The fact that tonus-stimulating drugs produce more marked effects on the uterine musculature following section of the extrinsic uterine nerves than under conditions of normal innervation also supports this assumption.

The experimental data bearing on the responses of the female genital organs to direct sympathetic and parasympathetic stimulation are not unequivocal. The muscular reactions vary in different animal species and under different physiologic conditions in the same species. The reactions of the pregnant uterus also differ from those of the non-pregnant uterus.

In experiments reported by Langley and Anderson (1895, 1896), sympathetic stimulation resulted in contraction of the musculature and vasoconstriction in the Fallopian tubes and the uterus in both cats and rabbits

The contractions involved both the longitudinal and circular muscles In favorable cases, the longitudinal shortening of the uterus was most striking When the stimulus was applied to the hypogastric nerve on one side only, they observed contraction of the uterine musculature and vasoconstriction only on that side Elliott (1905) also reported contraction of the Fallopian tube in response to sympathetic stimulation In experiments on dogs, Langley (1900) observed contraction of the uterus followed by marked relaxation in response to sympathetic stimulation Dale and Laidlaw (1912) also reported inhibitory effects of sympathetic stimulation on the uteri of virgin cats and guinea-pigs

Cushny (1906) advanced the hypothesis that the sympathetic nerves exert a diphasic effect on the uterus In virgin pregnant and multiparous rabbits, he observed powerful contractions of the whole uterus in response to sympathetic stimulation, followed by marked dilatation and inhibition of the spontaneous movements In virgin cats he observed only relaxation and in pregnant cats only contraction of the uterus in response to sympathetic stimulation On the basis of these findings he expressed the opinion that the hypogastric nerves include both sympathetic inhibitory and sympathetic excitatory fibers to the uterus Following the administration of ergochrysin, which presumably paralyzes the sympathetic motor mechanisms, he observed either short contraction followed by marked relaxation and inhibition of the spontaneous uterine movements or pure relaxation and temporary cessation of uterine activity in response to stimulation of the hypogastric nerves in non-pregnant rabbits and pregnant cats Dale (1906) observed similar responses to stimulation of the hypogastric nerves before and after the administration of ergotoxine Cushny also expressed the opinion that the hypogastric nerves normally exert no tonic influence on the uterine musculature since section of these nerves causes no change except a quick contraction followed by a return to the resting condition

The experimental data bearing on the effects of parasympathetic stimulation on the Fallopian tubes and the uterus afford no adequate basis for a positive conclusion In experiments reported by Langley and Anderson (1895 1896) and Dale and Laidlaw (1912) stimulation of the pelvic nerves in cats guinea pigs and rabbits elicited no recognizable responses in either the Fallopian tubes or the uterus Similar experiments have been carried out by other investigators with similar negative results Contraction of the uterus in response to parasympathetic stimulation also has been reported In view of all the data available it seems most probable that if the parasympathetic nerves exert an influence on the motility of the Fallopian tubes and the uterus it is generally inhibitory Lundberg (1925) advanced the opinion that the effect of the parasympathetic nerves on the uterine musculature is excitatory but this effect is usually concealed by the stronger effect of the sympathetic nerves

The response of the smooth musculature of the vagina to sympathetic stimulation very commonly differs from that of the uterine musculature particularly in non pregnant animals In the cat guinea pig and rat according to Gunn and Davis (1920) and Gunn and Franklin (1922) the vagina contracts in response to sympathetic nerve stimulation during coitus In experiments involving nerve stimulation they observed only contraction of the vagina in response to sympathetic stimulation accom-

panied by relaxation of the uterus in some cases and contraction of the uterus in others. The motor response to sympathetic stimulation or to adrenin, in their experiments, involved both the longitudinal and circular smooth muscle of the vagina and was most marked in the half of the vagina nearest the vulva. In experiments on cats reported by Van Dyke (1926), in which he studied the effect of ergotoxine on the response of the vagina to sympathetic stimulation, the normal responses obtained confirmed the findings of Gunn and his collaborators. Following the administration of ergotoxine, however, stimulation of the hypogastric nerve no longer elicited contraction of the vaginal musculature but either relaxation followed by contraction or complete relaxation. He interpreted these findings as supporting the assumption that the hypogastric nerves include inhibitory as well as motor fibers to the vagina.

Certain experimental data seem to support the assumption that pelvic nerve stimulation elicits inhibition of the smooth muscle of the vagina but the inhibitory response is not marked. Certain investigators, particularly Langley and Anderson, recognized no effect of pelvic nerve stimulation on the vagina.

The sympathetic nerves to the female genital organs include both vasoconstrictor and vasodilator fibers. Vasodilatation, particularly in the erectile tissue in the clitoris, may be elicited by parasympathetic stimulation. The data available do not support the assumption that the blood vessels throughout the genital organs are supplied with parasympathetic vasodilator fibers. Both the hypogastric and the pelvic nerves *include* visceral afferent components which are connected with receptors in various parts of the genital organs.

Genital Reflexes.—The spinal centers involved in the reflex control of the sex organs in the female, as in the male, are located in the sacral and upper lumbar segments of the spinal cord. The anatomic relationships of these centers and the afferent and efferent nerves involved are essentially identical in both sexes. The physiologic relationships also are comparable. Stimuli arising within the uterus, Fallopian tubes or Bartholin's glands may elicit reflex contraction of the smooth musculature of the genital tract through the lumbar center. Stimulation of the sensory end organs in the clitoris elicits reflexes through the sacral center which bring about vasodilatation and turgor of the erectile tissue in the clitoris. This reaction is comparable to erection in the male. Summation of the sensory impulses arising in the external genitalia also results in a discharge of efferent impulses from the upper lumbar center which brings about expulsion of the accumulated secretion of Bartholin's glands, a reaction which is comparable to the expulsion of seminal fluid in the male. In like manner, the summation of impulses arising in the external genitalia may result in the discharge of efferent impulses from the upper lumbar center through the hypogastric and uterine plexuses, which result in peristaltic contractions of the uterine musculature and expulsion of mucus from the cavity of the uterus.

Reflex uterine contractions elicited by stimulation of the mammary glands were not unknown to Hippocrates. Such reflex contractions may give rise to painful sensations. Uterine responses to stimulation of the breasts become more pronounced near the termination of pregnancy. Stimulation of the nipples elicits reflex reactions also in other parts of the

genital system In the rat and the mouse, according to Selye and McKeown (1934), suckling of the young results in long periods of diestrus which are interrupted by an estrus cycle only once in two or three weeks If the young are removed during a diestrus period the estrus cycle immediately returns to normal This disturbance of the sexual cyclicity during lactation seems to be independent of the secretory activity of the mammary glands but due to stimulation of the nipples It differs from copulation pseudopregnancy, which is caused by a single nerve stimulus in that its maintenance requires continuous stimulation of the nipples

A functional relationship between the erectile tissue in the genital organs and the cavernous tissue in the nasal mucosa has long been recognized Not infrequently the genital and nasal cavernous tissues react synchronously, *i e*, when either the genital or the nasal cavernous tissue becomes engorged the other also becomes engorged and when either one empties the other likewise empties Under certain conditions as observed by Sternberg (1929), either the genital or the nasal cavernous tissue may react independently of the other Zacharias (1941) has advanced certain data in support of the assumption that the hypophysis plays a role in the naso-genital relationship He has interpreted certain experimental and anatomic findings in rats as indicating that afferent impulses arising in the nasal mucosa elicit reflex reactions in the anterior hypophyseal lobe which in turn exert an influence on the genital organs probably through a hormonal mechanism

Reflex responses in the female genital organs may be elicited by impulses arising in adjacent viscera (Sinelnikow and Gugel-Morosowa 1937) or by afferent stimulation of somatic nerves Some of these reflexes are mediated through the genital centers in the lower lumbar and sacral segments of the spinal cord, others involve centers in the brain stem including the autonomic centers in the hypothalamus Theobald (1936) advanced certain data which seem to support the assumption that impulses emanating from the hypothalamus influence diverse genital functions including menstruation, ovulation, gestation and parturition

The Sexual Orgasm — The reactions involved in the sexual orgasm in the female are less definitely known than those involved in the corresponding phenomenon in the male According to Dahl (1916) the sexual orgasm involves comparable reactions in both sexes He assumed that the afferent impulses which give rise to the sensations involved arise in the female as in the male in consequence of the contraction of the smooth musculature of the genital tract Peristaltic contractions are normally initiated in the Fallopian tubes when sexual excitation is at its height These contractions are propagated to the uterus and vagina and are followed by rhythmic contractions of the striated sphincter vaginae muscles The afferent impulses involved in the sexual orgasm probably traverse the same nerves and central conduction pathways in the female as in the male

CHAPTER XX

INNERVATION OF THE SKIN AND ITS APPENDAGES

Anatomic Data.—Cutaneous Nerves.—The skin includes the sense organs through which most of the stimulating factors in the external environment influence the body; consequently, it is abundantly innervated through afferent nerves. The cutaneous vessels, other cutaneous muscular structures and the cutaneous glands also are innervated through autonomic nerve fibers which in general are associated with the afferent cutaneous nerves.

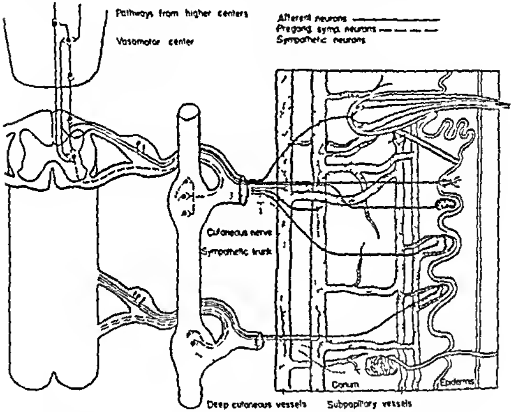


FIG. 69.—Diagrammatic illustration of sympathetic and afferent innervation of cutaneous structures.

As the cutaneous nerves approach the skin they form a coarse plexiform structure in the subcutaneous stratum. From this level smaller nerves penetrate the corium and form a plexiform meshwork at the border of the reticular and papillary strata. Rami arising from this plexus approach the epidermis and form a subepithelial plexus from which terminal branches of afferent fibers penetrate the deeper layers of the epidermis. The cutaneous nerves include both myelinated and unmyelinated afferent fibers. The terminal branches of most of the myelinated fibers also are unmyelinated. The autonomic fibers in the skin are mainly unmyelinated and of small caliber. Except in the cephalic area they are derived exclusively from the ganglia of the sympathetic trunks (Fig. 69). The autonomic innervation of the skin in the cephalic area also is mainly sympathetic. Parasympa-

thetic fibers probably reach the skin in the cephalic area but their cutaneous distribution is not fully known

Regeneration of sympathetic nerve fibers in the skin following lesions of cutaneous nerves or section of the nerves in the preparation of pedicle flaps takes place slowly The earliest return of sympathetic function in pedicle flaps, according to Kredel and Phemister (1939) becomes apparent only after sensory function has become reestablished Early and adequate sensory recovery, in their experience was usually but not invariably followed by sympathetic recovery

The afferent fibers terminate in relation to the specialized cutaneous sense organs and the hair follicles and in naked arborizations both in the corium and the deep layers of the epidermis The autonomic fibers terminate mainly in relation to the cutaneous vessels including capillaries the erector pili muscles and the cutaneous glands

Sympathetic nerve fibers are conveyed to the skin in cutaneous branches of the cerebrospinal nerves Those which traverse the spinal nerves join them via the corresponding gray communicating rami Those which reach the skin in the cephalic area join the corresponding cranial nerves mainly via the plexuses on the internal and external carotid arteries Since the preganglionic fibers which supply the cervical sympathetic ganglia are components of the upper thoracic nerves the spinal centers for the sympathetic innervation of the skin of the entire head neck upper extremity and the upper portion of the thorax are located in the upper thoracic segments of the spinal cord Since those which supply the sympathetic trunk ganglia in the lumbar and sacral segments are components of the lower thoracic and upper lumbar nerves the spinal centers for the sympathetic innervation of the skin of the lower extremities and the lower portions of the trunk are located in the lower thoracic and upper lumbar segments of the spinal cord In general the sympathetic innervation of the skin of the trunk is segmental, but Foerster (1929) has shown that preganglionic fibers arising in a given segment of the spinal cord may effect synaptic connections with sympathetic ganglion cells whose axons are distributed to the skin in several segments For example stimulation of the anterior root of the fifth thoracic nerve activates sweat glands from the fourth to the tenth thoracic segments

The simplest reflex arc involved in the reflex activity of cutaneous effectors may be conceived as follows the afferent limb consists of an afferent spinal nerve component which terminates peripherally in a cutaneous receptor, the efferent limb comprises a preganglionic neuron located in the intermediolateral cell column and a sympathetic ganglion cell located in the sympathetic trunk (Fig 69) If both afferent and efferent limbs are components of the same or adjacent nerves it may be assumed that the central connections are effected within the segments in question If, as in the case of effectors in the cephalic area the afferent and efferent limbs of the reflex arcs are connected with the central nervous system through widely separated nerve roots, the central reflex connections must be regarded as relatively complex Reflexes of a higher order carried out through afferent and efferent components of the same or adjacent spinal nerves also involve centers in the brain stem

Hair Follicles —The hair follicles are abundantly supplied with nerve fibers which form relatively dense plexuses around them These plexuses

include both myelinated and unmyelinated fibers The latter are mainly the unmyelinated terminal branches of myelinated fibers Many nerve fiber terminations undoubtedly occur in the connective tissue layers of follicles Terminal branches also penetrate into the epithelial layers The innervation of the hair follicles is essentially sensory but some fibers of sympathetic origin become involved in the perifollicular plexuses Unmyelinated fibers probably of sympathetic origin and myelinated fibers also terminate in the connective tissue papilla The former probably terminate in relation to the nutritive vessels in the papilla Nerve fibers in close relation to the sebaceous glands have been described but the data available do not warrant the conclusion that sympathetic fibers actually effect functional contacts with sebaceous gland cells Terminations of sympathetic nerve fibers in the erector pili muscles have been abundantly demonstrated

Sweat Glands —The sweat glands are simple tubular structures the ducts of which are provided with smooth muscle fibers which probably play a role in expelling the secretion These tubules are surrounded by delicate networks of unmyelinated fibers which lie close to the basement membrane Terminal branches of these fibers end in relation to the muscular elements and probably in relation to the secretory gland cells

In man sweat glands are distributed over the entire surface of the body but are more abundant and larger in certain areas than in others They are particularly abundant in the head face axilla palms, soles and genital region Perspiration usually is most profuse in these areas In many of the hairy mammals sweat glands occur only in restricted areas of the skin Cats have functional sweat glands only in the paw pads Young dogs have functional sweat glands in their paw pads These probably become nonfunctional as the animals grow older Pigs have functional sweat glands in the snout Rabbits, rats and mice probably have no sweat glands Certain other hairy mammals *e g*, the horse, have functional sweat glands over the entire surface of the body

Mammary Glands —The mammary glands are innervated through the lateral cutaneous rami of the second to the sixth intercostal nerves The nipple and areola are abundantly supplied with afferent fibers which terminate in cutaneous receptors, and sympathetic fibers which terminate in relation to the smooth muscle in the nipple and the adjacent superficial area The body of the gland is sparsely supplied with nerve fibers mainly sympathetic which reach it via the fourth fifth and sixth intercostal nerves The lateral cutaneous rami of these nerves give off mammary rami through which sympathetic fibers are distributed throughout the gland Sympathetic nerve fibers also reach the mammary gland along the course of the long thoracic artery and the anterior perforating branches of the intercostal arteries which supply the gland Within the mammary gland the sympathetic fibers terminate mainly in relation to the blood vessels and the smooth muscle which is sparsely distributed throughout the gland Certain physiologic data seem to indicate the existence of secretory fibers to the mammary gland but nerve fiber terminations in relation to mammary gland cells have not been demonstrated anatomically

Physiologic Data —**Hair Growth in Relation to Sympathetic Nerves** — Excessive growth of hair in a circumscribed area associated with a lesion of the nerves supplying it has been reported frequently This phenomenon

probably can be explained most satisfactorily on the assumption that the papillary blood supply has been increased due to partial or complete functional interruption of the sympathetic innervation of the vessels in question Loss of hair in a circumscribed area and failure of its restoration also is not uncommon This phenomenon undoubtedly involves reduction of the papillary blood supply due to peripheral vasoconstriction in the area in question

Leriche (1936) reported a case in which a spinal cord lesion at the level of the seventh thoracic segment resulted in persistent pain in this region and two bald areas on the occiput and the neck below it which resembled typical alopecia areata After other methods of treatment had failed, the pain was relieved by local anesthesia which was administered four times at intervals of two or three days After this treatment the growth of hair in the bald spots was restored Bergmann (1937) reported a case in which the injection of quinine hydrochloride and ethyl carbamate in a varicose vein for its obliteration was followed by the development of two typical areas of alopecia areata which persisted for about three months

In a study of the tissues in areas of alopecia areata, Levy-Frankel and Juster (1938) found a diminished number of patent capillaries and diminished caliber of those which were patent and evidence of spastic contraction of the arterioles They also cited additional evidence of localized vasoconstrictor hypertonicity as a factor in the etiology of alopecia areata The frequent occurrence of bald spots in patients with diseases in which the sympathetic nerves are known to be involved such as exophthalmic goiter scleroderma and vitiligo, also supports the assumption that sympathetic hypertonicity is a significant causative factor in spontaneous failure of hair growth Measures which result in overcoming peripheral vasoconstriction *e g*, mild local stimulation by mechanical chemical actinic or thermal agencies, not infrequently result in augmentation of hair growth, probably due to increased circulation through the papillary vessels

Regulation of Erector Pili Activity —The erector pili muscles contract in response to sympathetic stimulation *Generalized pilo-erection* is a common phenomenon associated with emotional excitation, due to the discharge of impulses from hypothalamic sympathetic centers Contraction of the erector pili muscles also is elicited reflexly by appropriate cutaneous stimulation, particularly exposure to cold Localized pilo-erection in an area of referred hyperalgesia associated with visceral disease is not an uncommon phenomenon It undoubtedly represents a reflex response to the stimulation of visceral afferent fibers in the area of the lesion, which gives rise to the referred sensory phenomena

Intracutaneous administration of acetylcholine and other drugs with nicotine like action elicits strong fleeting pilo-erector activity in the vicinity of the injection In experiments reported by Coon and Rothman (1940), this reaction was abolished by sympathetic nerve degeneration both in man and the cat but could be elicited in areas anesthetized by nerve block and in excised pieces of skin These results were interpreted as supporting the conclusion that the localized pilo-erector activity elicited by the drugs in question represents an axon reflex response mediated through the terminal branches of the sympathetic fibers supplying the erector pili muscles

Pilo-erection is essentially an involuntary response Individual cases

have been reported in which the hairs could be erected voluntarily. Lindsley and Sassaman (1938) reported a case in which voluntary erection of the hairs was accompanied by an increase in the cardiac rhythm, an increase in the rate and depth of respiration, dilatation of the pupils, a decrease in the galvanic skin resistance in areas rich in sweat glands, and a slight increase in blood pressure. These phenomena indicate a generalized sympathetic discharge. Involvement of impulses emanating from the cerebral cortex is indicated by characteristic changes in the brain potentials in the premotor area which preceded the peripheral autonomic changes and appeared to be associated with them. No evidence of conditioning could be detected.

Regulation of Sweat Secretion.—Unlike various other organs with sympathetic innervation, the sweat glands react only to a limited number of direct stimulating agents. Normally they are activated only by nerve impulses. Sympathetic denervation of a cutaneous area, except in certain portions of the head and face, results in complete and permanent cessation of perspiration except in the presence of stimulating agents which act upon the glands directly.

Localized lesions of the sympathetic trunks or their rami result in the cessation of thermoregulatory sweating in circumscribed areas. Such areas frequently are bounded by a zone of increased perspiration (List and Peet 1938, Guttmann 1940). Sympathetic denervation of extensive areas of the skin results in a marked increase in the sudomotor activity of the remaining areas which may be regarded as a compensatory thermoregulatory response. Denervated sweat glands, according to Gurney and Bunnell (1942), undergo no histologic changes and still retain the capacity to respond to excessive heat as well as to certain pharmacologic agents.

The secretory output of the sweat glands is determined in some measure by the cutaneous blood supply but these glands may exhibit secretory activity even in the absence of cutaneous circulation. Such activity is demonstrated by the finding that nerve stimulation elicits sweat secretion in a newly amputated limb. On the other hand, the administration of adrenin results in diminished sweat production due to the vasoconstrictor action of this hormone (Burn 1925). This is in full accord with the common observation that the production of sweat is diminished by chilling of the skin which brings about constriction of the peripheral blood vessels. Burn also demonstrated that pilocarpine, a potent sweat producing stimulant, is ineffective if the capillary dilatation brought about by the drug is prevented by section of the spinal nerve roots. In the absence of capillary tonus, pilocarpine is without effect on the cutaneous blood supply. Although the postganglionic fibers supplying the sweat glands remain intact, the drug has no effect on their secretory activity. Profuse sweating in man often accompanies a pallid skin, as in nausea or terror. On the other hand, the flushed skin of fever is characterized by the absence of perspiration. These facts indicate that the sweat glands are activated by impulses conducted by true secretory nerve fibers and that their activity may be quite independent of the functional state of the cutaneous blood vessels.

Concentration of the blood by extraction of water through the digestive system does not suppress perspiration completely. Profuse sweating sometimes occurs in cases of violent diarrhea and exhaustion even when a deficiency of water in the blood and tissues is indicated by profound thirst.

Abundance of water in the blood and tissues exerts no marked influence on the output of perspiration. The drinking of cold water in large quantities does not appreciably affect the secretory activity of the sweat glands. On the other hand the drinking of hot liquids, *e. g.*, hot tea, not infrequently calls forth sudden profuse perspiration.

Under physiologic conditions the most common causes of profuse sweating are high external temperature and muscular activity. In either case it may be regarded as thermoregulatory. Such sweating, according to List and Peet (1938), is centrally induced and is generalized. The appropriate autonomic centers in the brain stem are stimulated by the increased temperature of the circulating blood. The spinal centers involved in the innervation of the sweat glands also react to increased blood temperature as is demonstrated by the finding that, following transection of the spinal cord, perfusion of a portion of the cord below the section with blood heated to 45° C brings about profuse perspiration in the skin areas innervated from the portion of the spinal cord perfused.

Perspiration in response to external temperature which is limited to the area exposed to the high temperature may be regarded as reflex. The afferent impulses arising at the periphery are conducted centralward by sensory cutaneous fibers, probably the heat fibers, and the sweat glands are activated through their sympathetic nerves (Fig. 69). Such reflex activity may play a role in thermoregulatory sweating, particularly in response to external temperatures not sufficiently high to cause an appreciable increase in blood temperature.

Localized reflex sweating is not uncommon in visceral disease. The segmental perspiration in patients with pulmonary tuberculosis can be explained most satisfactorily on the assumption that impulses conducted from the site of a pulmonary lesion by visceral afferent spinal nerve components elicit reflex responses through preganglionic and sympathetic neurons involved in the innervation of the sweat glands in the corresponding cutaneous segment. Reflex sudomotor activity in localized areas of referred hyperalgesia associated with various visceral lesions may be explained on the same basis.

In many persons, particularly among the frail and the obese, profuse perspiration over the entire body may be elicited by exposure of a limited area, *e. g.*, an arm or a leg, to a high external temperature. In such cases, warming of a limited part of the body surface undoubtedly results in an increase in the temperature of the circulating blood sufficient to stimulate the appropriate centers in the brain stem. The occurrence of normal sweating in other parts of the body in response to exposure of an anesthetized cutaneous area to high temperature, as reported by Gurney and Bunnell (1942), supports this assumption.

The central sweat centers also react to changes in the acid-base balance of the blood. According to Hasama (1930), perfusion of the fourth ventricle with Ringer's solution or injection of this solution into the carotid artery results in profuse perspiration and a rise in body temperature. If the Ringer's solution is alcoholic it results in inhibition of perspiration and a rise in body temperature. These reactions probably are mediated through centers in the medulla oblongata, since they may be obtained after transection of the mesencephalon.

Perspiration may be elicited reflexly by various external stimuli other

than temperature. In experimental animals faradic stimulation of the brachial plexus elicits secretory activity of the sweat glands in both forelimbs. Unilateral faradic stimulation of the face, according to Deiden (1918), commonly elicits reflex sweating bilaterally. Painful stimulation if sufficiently intense may result in sudden profuse perspiration over the entire surface of the body. This reaction may be reflex in part, but emotional excitation undoubtedly constitutes a major factor. Purely reflex sweating probably is always localized.

Localized sweating may be elicited by direct stimulation of cutaneous nerves (Bickford, 1938). The local sweat response to faradic stimulation, according to Wilkins, Newman and Doupe (1938), represents an axon reflex mediated through postganglionic sympathetic fibers. It may be inhibited by the administration of atropine or augmented by the administration of prostigmine or blocked by the intradermal injection of novocain. It is independent of ganglionic connections, since it may be elicited following section of the cutaneous nerves. Local spread of the response also indicates that a given gland may be stimulated from different points, which supports the assumption that the terminal branches of the sympathetic fibers in question form a peripheral plexus.

On the basis of their experimental findings, Wilkins *et al.* have advanced the opinion that the sympathetic fibers which innervate sweat glands divide near their terminations into numerous fine branches which radiate through the skin in all directions. Every axon with its terminal branches therefore, may be regarded as an axon system. Since these systems overlap, stimulation at any given point may activate nearly all the glands in the immediate vicinity. A very small novocain wheal therefore does not entirely block the spread of impulses in any given direction from the point of stimulation but a larger one does.

The electrical resistance of the skin is closely coördinated with sweat gland activity. Richter and Levine (1937) reported a marked increase in electrical resistance in the skin of the palms and less in the skin on the volar surface of the hand in ten patients following cervical sympathectomy. They recommend the use of readings of the electrical resistance of the skin in the study of sympathetic disturbances in man since it requires little time, as compared with other methods, and may be repeated at frequent intervals with little inconvenience to the patient.

In certain individuals pungent odors and the ingestion of spicy foods elicit sweating in the face which has been called gustatory sweating. According to Wilson (1936), the sweat glands in the face are supplied with accessory secretory nerve fibers in addition to their sympathetic innervation which probably arise in the brain stem and join branches of the trigeminal nerve distal to its sensory ganglion. In some instances gustatory sweating seems to be mediated solely through the accessory fibers. The available data do not indicate that these fibers play a significant rôle in thermoregulatory sweating under physiologic conditions.

According to List and Peet (1938), gustatory sweating depends on reflex stimulation of cranial cholinergic fibers. Faint gustatory sweating occurs in many apparently normal persons. Gustatory hyperhydrosis has been reported, particularly by List and Peet, associated with auriculotemporal lesions and in other cephalic areas following cervical sympathectomy. They have regarded such exaggerated gustatory sweating as probably due to

local increased irritability of the cholinergic fibers Wilson (1936) advanced the opinion that excessive gustatory sweating may be related to a hyperactive condition of the sweat glands, as indicated by their response to pilocarpine

Psychic Stimulation of Sweat Secretion —Strong emotions, particularly anxiety and expectancy, not infrequently are accompanied by profuse perspiration even in persons in good health but more often in "nervous" individuals This need not be regarded as essentially pathologic Perspiration during emotional disturbances, however may assume a pathologic aspect Patients in whom such is the case usually also complain of other nervous disorders *e g*, tachycardia, gastric pains and headache Many individuals experience localized perspiration especially in the palms of the hands, and sometimes also on the soles of the feet during even minor emotional disturbances, such as embarrassment and perplexity Outbreaks of profuse perspiration without any apparent cause also have been observed in hysterical patients Emotional sweating is essentially of central origin but differs from thermoregulatory sweating in that its distribution may be localized

Response of Sweat Glands to Cerebral Stimulation —Cortical stimulation under certain conditions, results in excitation of the sweat glands This fact and the fact that perspiration is a common accompaniment of certain emotional states led certain of the earlier investigators to assume the existence of a cortical sweat center As a result of carefully executed experimental studies, Winkler (1908) concluded that certain cortical fibers arising in the frontal lobe influence perspiration and that these fibers descend through the subthalamic region and cerebral peduncles into the medulla oblongata These findings do not prove the existence of a cortical center for the functional regulation of the sweat glands Not a few investigators, including Deiden (1915) Karplus (1916) Bowing (1922 1924) and others have reported disturbances in the regulatory control of perspiration on the paralyzed side in cases of hemiplegia due to cerebral lesions Their observations do not prove that such disturbances are directly referable to the cerebral lesions in question Guttmann and List (1928) and Guttmann (1931) on the other hand have reported observations on patients with cerebral lesions which they interpreted as indicating the direct representation of the sweat glands in a large portion of the cerebral cortex, including a broad zone both anterior and posterior to the central sulcus and a limited area of the temporal lobe Guttmann (1931) also reported perspiration on the contralateral side in man in response to electrical stimulation of the cortex both in the precentral and postcentral gyri The onset of perspiration followed the beginning of stimulation after a latent period, and the secretory activity of the sweat glands continued for some time after stimulation of the cortex ceased Extirpation of the premotor cortex may be followed by excessive palmar sweating probably due to impulses emanating from centers in the hypothalamus which are released from cortical control (Darrow, 1937) In persons capable of voluntary pilo-erection this act usually is accompanied by secretory activity of the sweat glands (Sassman, 1938) These observations unmistakably prove that impulses emanating from the cerebral cortex exert an influence on the secretory activity of the sweat glands which is exerted through subcortical centers particularly the autonomic centers in the hypothalamus

Direct Influence of Spinal Centers on Sweat Secretion.—Recorded observations on the effect of organic lesions of the spinal cord on the functional activity of the sweat glands are somewhat contradictory. Normal perspiration as well as a decrease in sweat secretion or even its cessation in the paralyzed portion of the body has been reported following transverse lesions of the spinal cord. In a careful study of twelve paraplegic patients Bowing (1924) never observed complete absence of perspiration in the affected areas but usually found that the secretory activity of the sweat glands in these areas was somewhat diminished. Neither did he find a sharp line of demarcation between the areas of normal and diminished perspiration at the level of the spinal cord lesion in cases in which the lesion was located in the thoracic or lumbar region. This may be explained on the basis of the peripheral distribution of the preganglionic fibers involved in the innervation of the sweat glands. Most of these fibers, as stated above, terminate in more than one ganglion of the sympathetic trunk.

Unilateral lesions of the spinal cord not infrequently are followed by diminished perspiration in the affected region on the side of the lesion. Likewise, diseases which involve localized degeneration of spinal cord tissue, e.g., syringomyelia and poliomyelitis, also are accompanied by functional disturbances of the sweat glands in the affected area. Whether such disturbances involve a diminished or an increased output of perspiration depends on the exact site of the lesion and the character of the degenerative process. Destruction of cells in the intermediolateral cell column commonly results in localized anhidrosis.

Effect of Drugs on Sweat Secretion.—In general, drugs which affect the output of perspiration exert their influence through the nerve fibers supplying the sweat glands. Certain pharmacologic agents, e.g., pilocarpine, probably exert a direct stimulating effect on the glands. Langley (1922) observed an increased output of sweat on the hind paw pad of the cat following injection of pilocarpine after the sciatic nerve had undergone degeneration. This finding, which suggests a direct effect of pilocarpine on the sweat glands, has been corroborated by Burn (1925) and Hinsey and Cutting (1934). List and Peet (1938) concluded on the basis of clinical observations that pilocarpine, like acetyl beta methylcholine chloride, when administered subcutaneously in customary doses usually exerts no detectable direct action on the sweat glands but stimulates the endings of the cholinergic nerve fibers. Sweating elicited in this manner may be inhibited by the administration of atropine (Myerson *et al.*, 1937). Antipyretic drugs, e.g., the salicylates, probably cause perspiration due to their action on hypothalamic centers. Certain other drugs, e.g., strychnine and camphor, exert their sudorific effect on the spinal sweat centers. Muscarine and physostigmine bring about perspiration by their stimulating effect on the terminations of the nerve fibers which supply the sweat glands. Atropine paralyzes these nerve fiber terminations and therefore brings about cessation of perspiration.

Although adrenin is a powerful stimulant for other organs with sympathetic innervation, it does not bring about secretory activity of the sweat glands. It has even been found to inhibit spontaneous perspiration in certain neurotic patients and to diminish the sudorific effect of pilocarpine (Billigheimer, 1920). According to Freund (1920), adrenin, under

certain conditions may exert a stimulating influence on the sudorific mechanism. In certain cases, he found that areas of the skin which were treated with adrenin exhibited more profuse sweating than the adjacent areas while in the hot-air chamber. On the contrary, neither Langley (1922) nor Schilf and Mandur (1922) could detect an appreciable influence of adrenin injected into the hind-paw pads of cats on the secretory activity of the sweat glands, either with intact innervation or following section of the sciatic nerves. These observations are in accord with the later finding that the sympathetic fibers to the sweat glands are cholinergic. The chemical mediator liberated as a result of stimulation of cholinergic nerve fibers according to List and Peet (1938), may activate sweat glands even though the fibers in question do not effect direct contacts with the gland cells.

Nervous Influences in Mammary Function.—Nerve impulses play a role in the functional activity of the mammary glands but the manner in which the output of mammary secretion is influenced by them is not fully understood. The experimental studies carried out by the earlier investigators (Eckhardt 1858, Rohrig 1876, von Herff 1889, Basch 1893, [illegible] 1904) to determine the possible role of nerve impulses in the secretory activity of the mammary glands yielded results which vary widely and fail to [illegible] basis for definite positive conclusions. The results of all the experimental studies involving partial or complete denervation of the mammary gland indicate quite clearly that the secretory function of the [illegible] in large measure is independent of nervous regulation. Certain experimental data strongly suggest that the mammary secretion may be influenced, at least qualitatively, through the nerves which supply the mammary gland. According to Pfister (1901), denervation of the mammary glands in the rabbit results in no quantitative changes in the production of milk. In Kahn's (1925) experiments, unilateral section of the nerves supplying the mammary gland in the guinea-pig resulted in a qualitative difference in the milk secreted by the glands on the two sides. The fat and casein content of the milk produced on the side of the operation was appreciably increased. Cannon and Bright (1931) reported marked disturbances in lactation, but not its complete suppression, in cats and dogs which had been subjected to extirpation of the entire sympathetic trunks. In experiments involving 13 cats and 1 dog reported by Simeone and Ross (1938), partial or total sympathectomy resulted in no detectable changes in the histologic appearance of the mammary gland during gestation and lactation except possibly in one case. Labate (1940) reported the results of experiments involving 2 rabbits in which all the known sympathetic pathways to the uterus, tubes and ovaries had been removed and 3 control rabbits. All the rabbits were allowed to become pregnant. The controls were subjected to cesarean section on the twenty-fifth day of pregnancy, the sympathectomized ones on the twenty-seventh and thirty-second days respectively. The onset and duration of lactation were essentially the same in all the animals, and all showed normal reproductive instincts.

The development and growth of the mammary glands preceding puberty, their enlargement during gestation, the initiation of secretory activity and the beginning of milk production following parturition are correlated with changes in the genital organs and are brought about largely through the stimulating influence of hormonal substances produced by the internal sex

organs. Chemical stimuli and nutritive conditions also play a major role in milk production throughout the period of lactation. Nervous regulation, nevertheless, plays an important role in the flow of milk or the facilitation of its extraction from the mammary gland. The stimulus afforded by the sucking of the young in mammals, including the human species, is an important factor in increasing the output of milk at the beginning of lactation following parturition and in facilitating the extraction of milk throughout the lactating period. This stimulation of the nipple and areola elicits definite reflex reactions in the mammary glands which involve the movement of milk toward the outlet. These reactions in turn give rise to afferent impulses which result in more or less definite sensations.

The fact that unilateral stimulation of the nipple elicits reflex responses in both breasts indicates that the reflexes involved traverse the central nervous system. The afferent impulses are conducted to the spinal cord through the afferent fibers supplying the nipple and areola, the efferent impulses reach the glands through visceral efferent and sympathetic neurons. The reflex reactions in question involve mainly the smooth muscles in the nipple and areolar area and that which occurs in small quantity throughout the gland. Whether stimulation of the nipple and areola affects the output of milk through direct secretory fibers as yet is unknown.

Trophic Regulation of Skin.—The nutritive and functional states of the skin are constantly influenced through the sympathetic nerves and may be modified locally by sympathectomy. Regulation of the caliber of the cutaneous blood vessels and tissue spaces and capillary permeability undoubtedly is a major factor in trophic regulation.

In experiments reported by Kesselring (1936) the fluorescent dyes fluorescein and trypaflavin were injected into frogs which had been sympathectomized on one side. Following this treatment, the skin was examined with the aid of the ultrapak method. The cutaneous vessels were dilated on the sympathectomized side and the tissue spaces were larger on this side than on the other but the cells were stained more intensely on the normally innervated than on the sympathectomized side. These differences became more marked as the time interval following sympathectomy increased. Asher (1937) reported the results of experiments in which the reaction of sympathectomized skin to intracutaneous injections of histamine was compared with that of the normally innervated skin. In appropriate concentration histamine produced a large bleb in the sympathectomized skin but had no appreciable effect on the normally innervated skin. When the concentration of the drug was increased it produced a bleb also in the normally innervated skin which subsided much more rapidly than the one produced by the same concentration of histamine in the sympathectomized skin. Deprived of its sympathetic innervation the skin obviously becomes less resistant to the effect of histamine, possibly due to decreased permeability of the cutaneous capillaries. The dry scaly condition of the human skin, following sympathectomy, obviously is due mainly to cessation of the secretory activity of the sweat glands. Localized atrophy of the subcutaneous tissue and the connective tissue layer of the skin associated with chronic pulmonary tuberculosis (Pottinger, 1929) undoubtedly is a result of reflex vasoconstriction in the areas in question elicited by afferent stimulation at the [illegible] lesions.

CHAPTER XVI

INNERVATION OF CEPHALIC AUTONOMIC EFFECTORS

The extension of the sympathetic division of the autonomic nervous system into the head, the distribution of the sympathetic plexuses and nerves in the cephalic region and the anatomic relationships of the cephalic parasympathetic ganglia and nerves are described in Chapter I. In the present chapter, the anatomic relationships of the cephalic autonomic nerves will be treated only in relation to the autonomic effectors innervated through them.

Innervation of the Eye.—Extrinsic Nerves.—The eye is innervated through sympathetic, parasympathetic and sensory nerve fibers which reach it via the ciliary nerves. The short ciliary nerves arise from the ciliary ganglion, the long ciliary nerves from the nasociliary branch of the ophthalmic nerve. The smooth muscle of the eyelids (tarsal muscles) is supplied with sympathetic fibers which traverse the voluntary nerves to these organs. The sympathetic fibers in question are derived from the superior cervical sympathetic ganglion through the internal carotid and cavernous plexuses, the parasympathetic fibers arise in the ciliary ganglion. The afferent fibers supplying the sensory innervation of the eye are components of the nasociliary branch of the ophthalmic nerve.

The preganglionic fibers to the ciliary ganglion arise in the mid brain in a special group of visceral efferent neurons, the Edinger-Westphal nucleus, which is associated with the motor nucleus of the oculomotor nerve. They traverse the oculomotor nerve, the inferior division of which gives rise to the short motor root through which they reach the ciliary ganglion. The sympathetic fibers which traverse the ciliary ganglion are derived directly from the cavernous plexus on the internal carotid artery through a slender ramus which either reaches the ganglion as an independent sympathetic root or becomes incorporated in the long root which connects the ciliary ganglion with the nasociliary branch of the ophthalmic nerve and conveys the sensory fibers which traverse the ciliary ganglion to be distributed through the short ciliary nerves. The preganglionic fibers involved in the sympathetic innervation of the eye arise in the upper thoracic segments of the spinal cord. By stimulation experiments, Langley (1897) determined that the preganglionic fibers involved in the innervation of the dilator pupillæ muscles leave the spinal cord in the upper three thoracic nerves. Stimulation of the ventral roots of these nerves in the cat, in his experiments, regularly elicited dilatation of the pupil, whereas stimulation of the ventral roots of the lower cervical or fourth thoracic nerves did not. Most of the preganglionic fibers involved in the innervation of the dilator pupillæ muscles are components of the second thoracic nerve and most of those involved in the innervation of the nictitating membrane are components of the third thoracic nerve (Cordozo, 1933). The postganglionic sympathetic fibers which supply the dilator pupillæ muscle do not follow the course of the internal carotid artery all the way to the cavernous plexus. As early as 1878 François-Franck observed that the dog's pupil dilates in response to stimulation of the sympathetic fibers which pass through the middle ear

Destruction of the mucosa of the middle ear and the base of the foramen rotundum abolishes pupillary reactions elicited by stimulation of the cervical sympathetic trunk. The results of studies reported by Dieters (1927) and Zernik (1928) indicate clearly that the sympathetic oculopupillary fibers pass through the middle ear (on the promontory) in man as well as in the dog, cat and rabbit. The exact course of these fibers has been

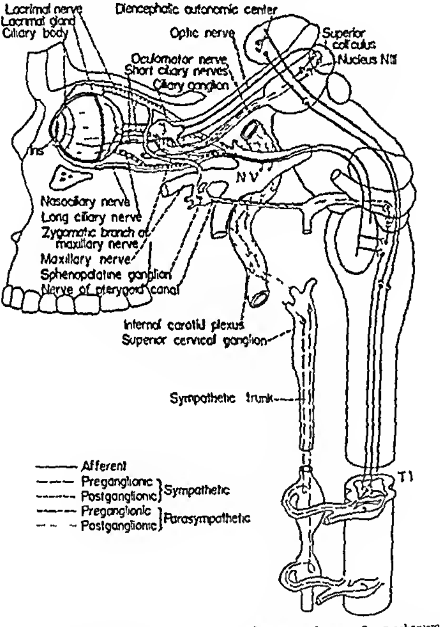


FIG 70.—Diagrammatic illustration of pupillary and accommodation reflex mechanisms

determined by the combined physiologic, anatomic and embryologic studies of many investigators. After leaving the superior cervical sympathetic ganglion they follow the internal carotid artery for a short distance and then deviate into the middle ear with the caroticotympanic fibers. Leaving the middle ear, they pass through the base of the cranium lateral to the nerve in the pterygoid canal and become associated with the cavernous

plexus Most of the sympathetic fibers to the eye do not actually pass through the ciliary ganglion Some of them reach the eye through the long ciliary nerves, others traverse the sympathetic root of the ciliary ganglion and become incorporated in the short ciliary nerves just distal to the ganglion The long ciliary nerves do not communicate with the ciliary ganglion but pass directly to the eyeball In general, these nerves comprise fibers which traverse the nasociliary nerve, including mainly afferent fibers for the sensory innervation of the eye and fibers which are derived directly from the plexus on the ophthalmic artery Those which innervate the dilator pupillae muscles belong to the latter group

Intrinsic Nerves —The short ciliary nerves, fifteen or more in number, arise from the ciliary ganglion and pass to the eyeball They convey parasympathetic fibers which arise in the ciliary ganglion and sympathetic and sensory fibers which join this ganglion through its sympathetic and sensory roots The short ciliary nerves penetrate the sclera and choroid to be distributed to the various parts of the eye Nerve fibers ramify in the sclera, but their exact distribution and mode of termination are unknown The cornea is richly supplied with sensory fibers which form an annular plexus around its periphery From this plexus, fibers pass into the cornea and ramify in the substantia propria, forming the fundamental or stroma plexus, from which fibers penetrate the elastic lamina and form a subepithelial plexus which gives off delicate fibers that ramify between the epithelial cells Some of these fibers extend out into the superficial layers Fibers arising from the annular and stroma plexuses extend into the substantia propria and come into close relation to the corneal cells The choroid and iris are supplied by fibers derived from both the long and short ciliary nerves These fibers traverse the perichoroidal lymph spaces where they form a plexus from which fibers are supplied to the choroidal blood vessels A second plexus is formed in front of the ciliary muscle from which fibers are supplied to the ciliary muscle and iris Ganglion cells have been described in both these plexuses On the basis of the results of the more recent anatomical studies the existence of ganglion cells in the ciliary body and iris in mammals seems highly improbable (Balado, 1927, Pines and Pinsky, 1932, Boeke, 1933) Unmistakable ganglion cells have been demonstrated in the plexuses associated with the intraocular muscles in birds (Clark and Small 1934) The nerve fibers which innervate the iris extend as far as the pupillary margin and supply both the muscles of the iris and its blood vessels According to Pines and Pinsky (1932), most of the nerve fibers which supply the muscles of the ciliary body and iris in mammals are myelinated and of larger caliber than those which supply the blood vessels, most of which are unmyelinated

The muscles of the iris and the ciliary body are abundantly supplied with nerve fibers The efferent innervation of the radial muscles of the iris is solely sympathetic, that of the circular muscle solely parasympathetic The efferent innervation of the ciliary muscles is mainly parasympathetic The results of various anatomic studies, including those of Pines and Pinsky (1932), Strebel (1935), Stotler (1937) and Clark (1937), afford no unmistakable evidence of a sympathetic innervation of these muscles Certain physiologic data seem to support the assumption that the radial components of the ciliary muscles are sympathetically innervated (Olmsted, 1944)

The intrinsic muscles of the eye probably are devoid of afferent innervation (Stotler, 1937, Clark, 1937, Hirano, 1941) The sclera and the cornea are abundantly supplied with afferent nerve fibers The nictitating membrane and the smooth muscle in the eyelids are innervated through sympathetic nerves but probably are devoid of parasympathetic innervation

Sympathetic Regulation of Ocular Functions —Stimulation of the cervical sympathetic trunk or the superior cervical sympathetic ganglion elicits dilatation of the pupil and retraction of the nictitating membrane According to Bishop and Heinbecker (1932) these reactions are mediated through the largest preganglionic fibers in the cervical sympathetic trunk i e , those whose threshold of stimulation is lowest, consequently, they may be called forth by stimuli which are too weak to excite the fibers of higher threshold which subserve other physiologic functions Section of the cervical sympathetic trunk or extirpation of the superior cervical sympathetic ganglion results in certain definite ocular changes Purfour and Petit (1772) were not unfamiliar with these phenomena Following section of the cervical sympathetic trunk in the cat they observed that the eye was somewhat sunken the rima oculi narrow, the pupil constricted the nictitating membrane extended and the vessels of the conjunctiva dilated Their observations were later corroborated by those of other investigators These ocular changes are now familiar clinical phenomena following cervical sympathectomy in man According to Mutch (1936) the sunken position of the eye is only apparent The narrowing of the palpebral fissure is caused by drooping of the upper eyelid and slight elevation of the lower due to relaxation of the smooth muscle in the eyelids

The intra-ocular pressure increases somewhat following cervical sympathectomy due to the hyperemia resulting from section of the vasoconstrictor fibers but later gradually returns toward the preoperative level as the blood vessels regain their inherent tonus (Lanksz 1931) Histologic studies of the retina following section of the cervical sympathetic trunk particularly in the frog revealed no significant changes (Ducret and Kogo 1931)

In experiments on rabbits reported by Chervet (1936) the cornea of an eye deprived of its sympathetic innervation was less resistant to the effect of quartz light than the cornea of the normally innervated eye The corneal injury produced by quartz light also healed less promptly in the sympathectomized eye than in the normal one These results seem to indicate a trophic influence of the sympathetic nerves on tissue devoid of circulation

Budge (1855) who studied the pupillary reactions under various experimental conditions, observed that the dilator pupillae muscles were atonic following section of the cervical sympathetic trunk He concluded therefore that this operation interrupts the dilator fibers He first determined that these fibers emerge from the spinal cord in the upper thoracic segments and concluded that this portion of the spinal cord includes a center for pupillary reactions which he designated the ciliospinal center

Langendorff (1909) reported the results of experiments in which section of the cervical sympathetic trunk, following section of the spinal cord in the upper cervical region resulted in constriction of the pupil Lateral hemisection of the cervical spinal cord in the rabbit was followed by temporary constriction of the corresponding pupil but, when the cervical

sympathetic trunk also was cut, the pupillary constriction remained permanent. He could explain these results only by assuming the existence of a ciliospinal center in the upper thoracic segments of the spinal cord. This assumption has been amply supported by the results of later investigations.

The diencephalon also includes centers from which impulses reach the dilator pupillae muscles via the sympathetic nerves. Ingram, Ranson and Hannett (1931) have shown that dilatation of the pupil may be elicited by stimulation of various other parts of the brain stem. In their experiments, this reaction was regularly elicited by stimulation of any point in the tegmentum of the mesencephalon and pons. This does not prove that the pupillary response, in every instance was called forth by impulses emanating from neurons located at the point stimulated but the stimulus probably affected descending visceral fibers which are widely scattered in the tegmental portion of the brain stem. The impulses in question reach the cervical sympathetic through neurons in the ciliospinal center. Keller (1932) demonstrated that activity in the ocular structures which are innervated by sympathetic fibers can be elicited by physiologic stimuli in animals following transection of the brain stem at the middle level of the mesencephalon. While this result shows that the sympathetic tonus of the eyes due to physiologic stimuli is not wholly dependent on the functional integrity of centers above the middle level of the mesencephalon, it neither adds to nor detracts from the evidence which has given rise to the theory that the tonic sympathetic control of the eye is mediated through an autonomic center in the diencephalon.

Reflex dilatation of the pupil may be elicited by afferent impulses arising in any part of the body. Whether somatic or visceral in origin the impulses in question are conducted upward in the lateral funiculus of the spinal cord on the same and the opposite side (Harper and McSwiney 1937). Those which are conducted upward on the contralateral side cross the medial plane in the segment just above the one in which they enter the cord. McSwiney and Suffolk (1938) also advanced evidence of a segmental distribution of the peripheral afferent neurons which conduct pupillodilator impulses from the abdominal viscera.

Dilatation of the pupil, separation of the eyelids, and retraction of the nictitating membrane may be brought about in experimental animals, by stimulation of the cerebral cortex. This does not prove that the smooth musculature of the eye and other orbital structures are directly represented in the cortex. Braunstein (1894) attempted to explain pupillary dilatation following cortical stimulation is a result of relaxation of the sphincter pupillæ due to inhibition of the pupillary center in the oculomotor nucleus. Karplus and Kreidl (1911) did not admit the validity of this explanation. In their experiments the pupil failed to dilate in response to stimulation of the cortex or the autonomic center in the diencephalon following section of the cervical sympathetic trunk. They also elicited reflex dilatation of the pupil following section of the oculomotor nerve although the pupil was already dilated. Their experimental data show clearly that active pupillary dilatation may be elicited by cortical stimulation and that the efferent impulses are conducted through the cervical sympathetic trunks. These data also prove that the cortical impulses in question are mediated through autonomic centers in the diencephalon, and that they are conducted by

the same pathways in the spinal cord as impulses arising from direct stimulation of the diencephalic centers. Destruction of the hypothalamus on one side abolishes the effect on the cervical sympathetic of stimulation of the frontal cortex on the same side but not of stimulation of the frontal cortex on the opposite side.

In experiments reported by Cate (1934), dilatation of the cat's pupil was elicited in a quiet room by weak sounds. Noises raised the threshold of stimulation. This reaction was not abolished by extirpation of the cortex in either the motor or striate areas. The disturbance of the reflex due to cortical ablation subsided less rapidly following removal of the auditory cortex than following removal of either the motor or the striate cortex.

Parasympathetic Regulation of Ocular Functions.—Stimulation of the oculomotor nerve brings about constriction of the pupil by active contraction of the constrictor pupillæ muscle. Section of the oculomotor nerve is followed by dilatation of the pupil due to the absence of tonus in the sphincter in the presence of normal tonus in the dilator pupillæ muscle. Sympathetic stimulation following section of the oculomotor nerve, brings about still further pupillary dilatation due to active contraction of the dilator pupillæ muscle. Constriction of the pupil also may be elicited reflexly by stimulation of the optic chiasm, the optic tract or the superior quadrigeminal brachium. Ranson and Magoun (1933) also reported pupillary constriction in response to stimulation of the pretectal region, the posterior commissure and the fibers emerging from the posterior commissure which arch around the ventral aspect of the central gray matter at the upper end of the cerebral aqueduct. Stimulation of the superior colliculus, in their experiments, did not elicit pupillary constriction.

The light reflex is mediated through the parasympathetic innervation of the muscles of the iris. It is elicited by stimulation of retinal receptors. The pupil dilates in darkness or dim light and contracts to a pin point when the retina is strongly illuminated. The functional value of these reactions is obvious. Enlargement of the pupil in dim light increases the total illumination of the retina, thereby increasing visual power; constriction of the pupil in strong light also aids vision by decreasing the illumination of the retina and diminishing spherical aberration. The effective stimulus which brings about this reflex is the light falling on the retina; the afferent fibers involved traverse the optic nerve. Inasmuch as part of the optic nerve fibers cross in the optic chiasm, the light reflex involves both eyes. The efferent fibers involved are preganglionic components of the oculomotor nerve and postganglionic fibers arising in the ciliary ganglion. The central connections probably are effected mainly in the pretectal region. In the monkey and the cat, according to Magoun *et al.* (1936), the afferent fibers involved in the light reflex do not enter the superior colliculus but deviate from the superior quadrigeminal brachium into the pretectal region where they effect connections with neurons whose axons enter the Edinger-Westphal nuclei. Some of these fibers cross the medial plane in the posterior commissure and ventral to the cerebral aqueduct in the immediate vicinity of the oculomotor nuclei. Injury to either the afferent or the efferent path diminishes or destroys the reflex. It also is lost in some cases in which neither of these paths appears to be injured. For example, in tabes dorsalis and general paresis the pupil is constricted and does not react to light (Argyll-Robertson pupil) but the

accommodation reflex remains intact. This phenomenon suggests that the central connections involved in the light reflex differ from those involved in the accommodation reflex. The reflex reaction of the sphincter pupillæ to light probably is greatest when the retina is stimulated at or near the fovea and varies directly with the intensity of the light and the area illuminated (Abelsdorff and Feilchenfeld, 1904).

Data which support the assumption that the constrictor muscles of the iris may be influenced by impulses emanating from the cerebral cortex are not wanting. In experiments reported by Hare *et al.* (1935), stimulation in the lateral wall of the lateral ventricle at the level of the rostral border of the lateral geniculate body resulted in constriction of the pupil, probably due to stimulation of efferent fibers of cortical origin which effect synaptic connections in the pretectal region. Waller and Barris (1937) reported experiments in which unilateral ablation of an area of the occipital cortex at the lower end of the posterior lateral gyrus in cats resulted in inequality in the size of the pupils, the one on the side opposite the lesion being larger than the other. Impulses emanating from the occipital cortex which influence the size of the pupil probably are conducted through corticopretectal fibers. In experiments reported by Hodes and Magoun (1942), stimulation in the rostral portion of the cerebral hemisphere in the cat resulted in pupillary dilatation. This reaction is regarded as due to parasympathetic inhibition, since it could not be obtained following interruption of the parasympathetic innervation of the iris. Stimulation of the anterior portion of the gyrus cinguli and adjacent cortical areas, in their experiments, elicited pupilloconstrictor responses.

Cates (1934) reported the establishment of conditioned pupilloconstrictor reflexes in cats on the basis of the unconditioned light reflex. Such conditioned reflexes could not be built up following ablation of the visual cortex.

The accommodation reflexes are mediated mainly through the parasympathetic innervation of both the ciliary muscles and the circular muscle of the iris. Contraction of the ciliary muscle in the act of accommodation is accompanied by simultaneous contraction of the sphincter pupillæ. Thus when the eye is accommodated for near vision, the pupil is constricted. The reaction of the constrictor pupillæ in this instance in reality represents an associated movement in which the act of accommodation carries with it the constriction of the pupil, probably due to activation of neurons in the mid brain which control the sphincter pupillæ by the stimulus which activates the neurons which control the ciliary muscles. The accommodation reflex also is accompanied by associated activity of the extrinsic muscles of the eye. Under normal conditions every act of accommodation for near vision is accompanied by convergence of the eyes due to contraction of both medial rectus muscles. The sympathetic innervation of the eyes probably plays no direct part in accommodation for near vision.

Accommodation for distant vision has very commonly been regarded as a passive process. Certain data, particularly the experimental data reported by Olmsted and Morgan (1941) and Olmsted (1944), support the assumption that flattening of the anterior surface of the lens in some degree may be brought about reflexly through the sympathetic nerves or by direct sympathetic stimulation. In experiments on rabbits, cats, dogs and monkeys, as reported by Olmsted, stimulation of the sympathetic nerves

to the eye resulted in flattening of the lens. In some of these experiments reflex inhibition of the parasympathetic nerves was ruled out by section of the oculomotor nerve and the roots of the upper thoracic spinal nerves or removal of the ciliary ganglion. The flattening of the lens in these experiments, has been regarded as the result of tension on the lens capsule caused by contraction of the radial ciliary muscles elicited by sympathetic stimulation. Momentary responses of the same order have been elicited both in animals and human subjects by startle. The reduction in the curvature of the anterior surface of the lens induced by sympathetic stimulation, as Olmsted pointed out, is relatively small as compared with the increase in curvature induced by parasympathetic stimulation.

The ciliary muscles also respond reflexly to a variety of afferent impulses other than those of light. Pearcy and Allen (1927) reported reduction of 2 to 5 diopters in accommodation in human subjects in response to increased enteric pressure produced by inflating a balloon in the stomach or the distal portion of the colon. The fundus vessels also were dilated and the retina became edematous after fifteen to twenty minutes.

Synergic Action of Sphincter and Dilator Pupillae.—Under normal conditions the sphincter and dilator muscles of the iris are maintained in a state of tonic activity by impulses received through their respective motor fibers. They constitute a synergic mechanism which responds promptly and smoothly to stimulation of either set of nerves. The synergic action of these muscles, at least in a measure, is comparable to that of the flexor and extensor muscles around a joint. The explanation of specific pupillary reactions is complicated by the fact that dilatation of the pupil may be brought about either by contraction of the dilator muscle or relaxation (inhibition) of the sphincter, while constriction of the pupil may be brought about either by contraction of the sphincter or relaxation of the dilator muscle. On the other hand, the contraction of one of these muscles may always be accompanied by inhibition of the other, as is assumed to be the case with the flexor and extensor muscles of the limbs. Certain experimental data strongly suggest that dilatation of the pupil may normally be brought about by a double action of this sort, i.e., contraction of the dilator muscle followed by inhibition of the sphincter (Anderson, 1903). Alterations in the size of the pupil occur not only in response to the effect of light on the retina and in the accommodation reaction but also under a variety of other conditions both normal and pathological. In sleep the pupils are constricted and the eyes rotate upward and outward. Pupillary constriction, in this case, may be due to inhibition of the tonus of the dilator muscle or increased tonicity of the sphincter. The assumption that the tonicity of the sphincter pupillae is increased during sleep is favored by the fact that experimental data are not wanting which indicate that, during the waking state, the mid-brain center which controls the sphincter pupillae is kept in a state of inhibition by a constant influx of sensory impulses. Most of these inhibitory impulses are cut off during sleep, consequently the sphincter tonus is increased. Emotional states also are accompanied by changes in the size of the pupil which aid in producing the facial expressions characteristic of the emotional state existing at the moment. For example, deep emotions of pleasure as well as fear are commonly accompanied by pupillary dilatation. This reaction may be explained either as the result of stimulation of the dilator muscle or tonic inhibition of the

sphincter. In favor of the former explanation is the fact that strong emotional states are accompanied by general sympathetic stimulation. Psychic or emotional mydriasis, as pointed out by Ingalls (1923), is closely allied to the typical reflex contraction of the dilator pupillæ muscle ordinarily elicited by cutaneous stimulation. Like many other effectors which are innervated through the autonomic system, this muscle responds to all manner of psychic stimuli as well as to a great variety of sensory stimuli. It is not inconceivable that the same afferent impulses which give rise to the emotional state also inhibit the pupillary center in the mid-brain. Lieben and Kahn (1930) have shown that emotional pupillary reactions, following sensory stimulation, are abolished by deep anesthesia and following section of the brain stem above the mesencephalon. On the basis of these findings, they advanced the opinion that emotional pupillary reactions depend on the functional integrity of the cerebral cortex.

Relative Importance of Sphincter and Dilator Mechanisms.—Although the sphincter and dilator pupillæ muscles sustain the relation of synergists to each other, the former must be regarded as of much greater functional importance than the latter. The dilator pupillæ muscle is closely related functionally to other visceral structures which are innervated through the thoracolumbar autonomic outflow. The sphincter pupillæ is more highly specialized than the dilator both structurally and functionally and is strictly a part of the visual organ. The dilator pupillæ is not essential for vision, although it may play a minor role in the visual functions of the eye. Unlike the sphincter, it is extremely responsive, at least in the higher vertebrates, to stimuli which elicit general sympathetic reactions. Whatever effect it has on the accommodation and light reflexes is exerted mainly by virtue of the tonus which is constantly maintained in it through its sympathetic innervation.

Both these muscles are of epithelial origin. The sphincter muscle is stronger than the dilator and contracts more rapidly. In the lower vertebrates, *e. g.*, fishes and Amphibia, the sphincter pupillæ is pigmented and itself reacts to light. In the higher vertebrates, as pointed out above, the light reflex is mediated by a relatively complex reflex mechanism. In man, it is present at or before birth, while the accommodation reflex does not appear until the fifth month of postnatal life (Ingalls, 1923). The pupil exhibits considerable variation in size under the same conditions of illumination. Very early and also late in life, the pupil is relatively small, probably due to the relatively weak antagonism of the dilator muscle during these periods. Albino and blue eyes normally exhibit smaller pupils than dark eyes. This may be regarded as a normal ocular reaction to light. Under ordinary conditions, the ciliary and sphincter muscles usually react together. The pupil, however, may react independently to the amount of light entering it; consequently, there may be myosis in distant vision under conditions of strong illumination and mydriasis in near vision under conditions of weak illumination. The dilator pupillæ plays only a secondary role in these reactions which are mainly expressions of tonus changes in the sphincter muscle.

Action of Drugs on Iris and Ciliary Body.—The dilator pupillæ, like other smooth muscle with sympathetic innervation, contracts in the presence of adrenin. Atropine, homatropine and cocaine exert a mydriatic effect. In animals in which morphine causes excitement, *e. g.*, the cat, it

also causes dilatation of the pupil Physostigmine and pilocarpine are well known myotics Regarding the site of the action of these drugs, it may be stated that adrenin stimulates the sympathetic fiber terminations in the dilator muscle, while atropine paralyzes the parasympathetic fiber terminations in the constrictor muscle Physostigmine and pilocarpine probably cause myosis by stimulating the endings of the same parasympathetic fibers Cocaine probably first stimulates mainly the endings of the sympathetic fibers in the dilator muscles and in stronger doses paralyzes the endings of the parasympathetic fibers in the sphincter pupillæ The stronger mydriatics paralyze the ciliary muscle as well as the sphincter pupillæ, thus destroying the power of accommodation In the mydriasis of cocaine and the myosis of physostigmine the light reflex is not abolished The stronger myotics stimulate the ciliary muscle, consequently, the eye exhibits a condition of forced accommodation during the period of their activity

Parasympathetic denervation of the eye results in a marked increase in the sensitivity of the sphincter pupillæ to acetylcholine and certain other parasympathomimetic substances, *e g*, acetyl beta-methylcholine chloride and carbaminoylcholine In experiments reported by Keil and Root (1941 1942), sensitization of the iris sphincter in the cat to acetylcholine reached its maximum about five days after parasympathectomy and continued at approximately the same level until the eighteenth day and then gradually subsided, reaching a minimum low level about the thirty-fifth day following parasympathectomy Their data support the assumption that the decrease in acetylcholine sensitivity following a period of maximum sensitization is associated with increased choline esterase activity

Regulation of the Nictitating Membrane —Projection of the nictitating membrane following cervical sympathectomy in experimental animals is a phenomenon observed by many investigators Slight projection of this membrane also occurs in man following cervical sympathectomy

Zernick (1928) advanced certain data which seem to demonstrate the sympathetic innervation of the muscles which retract the nictitating membrane in the cat He also pointed out that this membrane includes two groups of muscles one of which brings about its retraction and the other its protrusion Stibbe (1928) also described two groups of muscles in the nictitating membranes in Amphibia birds and mammals and concluded *that two distinct neuromuscular mechanisms are involved* in the movements of these membranes Bishop and Heinbecker (1932) reported retraction of the nictitating membrane in the rabbit in response to cervical sympathetic stimulation According to Rosenblueth and Bard (1932), the smooth muscle which retracts the nictitating membrane in the cat is innervated by sympathetic fibers and protrusion of this membrane is brought about by contraction of the outer fibers of the external rectus muscle which insert in its inferior horn According to their observations, protrusion of the nictitating membrane may be accomplished by the contraction of these fibers independently of outward rotation or retraction of the eyeball Cervical sympathectomy combined either with section of the abducens nerve or deep anesthesia completely paralyzes the nictitating membrane in the cat

In experiments on cats and dogs under choloralose or dial anesthesia, reported by Brunton (1935), ephedrine in doses of 0 3 to 0 5 mg per kilo

of body weight resulted in retraction of the nictitating membrane and eyelids without marked dilatation of the pupil This resulted in apparent exophthalmos without protrusion of the eye in some animals and slight protrusion in others The apparent exophthalmos persisted longer than the rise in blood pressure caused by the drug All these effects of ephedrine could be obtained following cervical sympathectomy but not following administration of ergotoxine

Contraction of the nictitating membrane in cats elicited by afferent stimulation of the sciatic nerve, in experiments reported by Rosenblueth and Schwartz (1935) was increased following section of the vagi and denervation of the carotid arteries The effects of simultaneous stimulation of two afferent nerves also were summated in the reflex response of the nictitating membrane Liu (1935) reported summation of the effects of sympathetic nerve impulses sympathin from other sources and adrenin applied simultaneously in the responses of the nictitating membrane in cocainized cats A subliminal application of either of these stimulating agents is capable of increasing the response of the nictitating membrane to either of the others or to both in combination

In cats under urethane anesthesia as reported by Watkins (1938) distention of the urinary bladder or the rectum elicited reflex responses of the nictitating membrane In some instances the membrane contracted in response to distention of the bladder but usually it relaxed and showed a positive rebound when the bladder was emptied Dilatation of the rectum usually elicited relaxation of the nictitating membrane, dilatation of the anal sphincter elicited contraction The afferent impulses in question were conducted centralward through both the hypogastric and the pelvic nerves

Innervation of the Lacrimal Gland —The parasympathetic innervation of the lacrimal gland is derived from the sphenopalatine ganglion, its sympathetic innervation from the superior cervical sympathetic ganglion The parasympathetic fibers traverse the maxillary nerve its zygomatic ramus the zygomatico-temporal branch of this ramus and the lacrimal nerve which is joined by the zygomatico-temporal The sympathetic fibers traverse the internal carotid plexus and reach the lacrimal gland through the ophthalmic nerve and its lacrimal ramus

Lacrimal Secretory Regulation —The regulatory influence of the parasympathetic innervation of the lacrimal gland in its secretory activity has been demonstrated both experimentally and clinically Section of the lacrimal nerve distal to the point at which the zygomatico-temporal nerve joins it (Demtschenko, 1872) or section of the greater superficial petrosal nerve (Ford, 1933) abolishes reflex lacrimation Goldzieher (1895) also pointed out that the functional activity of the lacrimal gland is disturbed immediately after paralysis of the facial nerve due to a lesion proximal to the geniculate ganglion This observation was confirmed by Clapp (1897) and other more recent investigators The paroxysmal lacrimation which is associated with facial palsy, according to Ford (1933) can be explained most satisfactorily on the assumption that some of the preganglionic secretory fibers which formerly effected synaptic connections with ganglion cells whose axons innervate salivary glands on regeneration effect connections with ganglion cells whose axons innervate the lacrimal gland

Stimulation of the sympathetic nerves supplying the lacrimal gland

results in increased lacrimal secretion (Wolferz 1870, Reich 1873) but section or paralysis of these nerves has no marked effect on the normal functioning of the gland. Muller and Dahl (1910) regarded the existence of sympathetic secretory fibers to the lacrimal gland as highly probable, although sympathetic fibers probably play no important role in reflex lacrimal activity. In experiments reported by Maes (1938), cervical sympathectomy in cats resulted in no immediate change in lacrimal secretory activity but eleven days or longer after the operation the sensitivity of the lacrimal gland to acetylcholine, pilocarpine and adrenin was increased, probably due to increased permeability of the gland cells.

Innervation of the Nasal and Oral Mucous Membranes.—The mucous membranes of the nares, including the paranasal sinuses, and the oral and pharyngeal cavities are innervated through both sympathetic and parasympathetic nerves and afferent components of both cranial and spinal nerves. The sympathetic fibers are derived mainly from the superior cervical sympathetic ganglia *via* the plexuses on the internal and external carotid arteries and their branches. The parasympathetic fibers are derived mainly from the sphenopalatine, otic and submaxillary ganglia through peripheral rami some of which reach the mucous membranes directly and others of which join peripheral branches of the corresponding cranial nerves (see p. 30). The afferent fibers are mainly components of the trigeminal nerves. Afferent components of the glossopharyngeal and vagus nerves reach the mucous membrane particularly of the tongue and the pharynx. Some afferent vagus components also join the plexuses on the internal and external carotid arteries to be distributed to various cephalic areas (Kuntz, 1934). As has been demonstrated in experimental animals (cats), afferent components of the upper thoracic spinal nerves traverse the inferior cervical sympathetic ganglion, join the plexus on the common carotid artery and extend cephalad in it. Most of these fibers continue cephalad in the internal and external carotid plexuses and probably reach their terminal distribution in association with the sympathetic fibers which traverse these plexuses (Kuntz, 1934). The presence of myelin degeneration in Marchi preparations of nasal and nasociliary nerves following section of the roots of the upper four thoracic nerves, as observed by Christensen (1934), indicate that some of the afferent components of the thoracic nerves which extend into the cephalic region actually reach the mucous membranes of the nose and the paranasal sinuses. Clinical data which support the assumption that afferent spinal nerve fibers reach the nasal and oral mucous membranes in man via the plexuses on the carotid arteries are not wanting.

Functional Regulation of the Nasal and Oral Mucous Membranes.—The mucous and serous glands in the nasal, oral and pharyngeal mucous membranes, like the parotid and maxillary glands, do not secrete continuously but are activated reflexly by a wide variety of unconditioned and conditioned stimuli. The oral and pharyngeal glands, according to Montgomery and Stuart (1936), respond much more readily to mechanical stimulation of the oral mucosa than the larger salivary glands. Their thresholds for weak food and taste stimuli, with the exception of acid, are lower than those of the parotid and submaxillary glands but the latter react more intensely than the former to strong food and taste stimuli. During periods of water deprivation the glands in the mucous membranes

maintain their normal secretory rate longer than the parotid and submaxillary glands

Reflex activation of the glands in the mucous membranes probably is mediated mainly through the parasympathetic nerves The vasomotor reactions in the mucous membranes are mediated mainly through the sympathetic nerves

Observations on the effects of nerve stimulation on ciliary activity in the upper respiratory tract including the nares particularly in the frog have been reported by various investigators including McDonald *et al* (1927), Pohle (1931) and Lucas (1935) According to Lucas' account, sympathetic stimulation has no effect on the movement of the cilia on the frog s palate but parasympathetic stimulation elicits acceleration of ciliary movement in this area

Experimental data reported by Burkart (1936) support the assumption that the sympathetic nerves exert a calorogenic influence on the mucous membranes By means of differential and absolute thermoelectric measurements, in animals which had been subjected to unilateral cervical sympathectomy, he found the mucous membranes generally warmer on the sympathectomized side than on the other but during sympathetic stimulation the mucous membrane became warmer on the normally innervated side than on the sympathectomized side The calorigenic influence probably is effected through the sympathin liberated

Although the blood vessels in the cavernous or erectile tissue in the nasal mucosa are innervated by the same nerves as those in the adjacent mucous membrane this tissue does not always conform to the vascular state of the adjacent mucosa The cavernous tissue frequently becomes engorged while the mucous membrane is relatively ischemic and frequently contracts while the mucous membrane is markedly hyperemic (Sternberg 1929) Application to the nasal mucosa of certain pharmacologic agents which regularly cause hyperemia of the mucous membrane results in contraction of the cavernous tissue, consequently, it has been assumed that the vessels of the cavernous tissue react to nerve stimulation according to a mode which differs from that of the vessels in the adjacent mucous membrane This assumption is unwarranted due to the anatomic relationships of the vessels in question

According to Zuckerkandl s (1893) account, the capillary bed in the cavernous tissue is interposed between veins, whereas the capillary bed in other parts of the nasal mucosa is interposed between arteries and veins The blood enters the cavernous bodies from the subepithelial capillary plexus and the more superficial portions of the periglandular plexus In view of this arrangement it seems not improbable that reflex stimulation which elicits vasoconstriction in the nasal mucosa might prevent emptying of the capillary bed in the cavernous tissue by contraction of the veins which drain it Reflex stimulation which elicits vasodilatation in the nasal mucosa on the contrary probably results in contraction of the cavernous tissue due to facilitation of the outflow of the blood by the dilatation of the efferent veins

Innervation of the Salivary Glands —The major salivary glands, the parotid, submaxillary and sublingual, the ducts of which lead into the oral cavity are innervated through both parasympathetic and sympathetic nerves Their parasympathetic innervation is derived from the otic and

submaxillary ganglia, their sympathetic innervation from the superior cervical sympathetic ganglia *via* the plexuses on the internal and external carotid arteries (Fig 71)

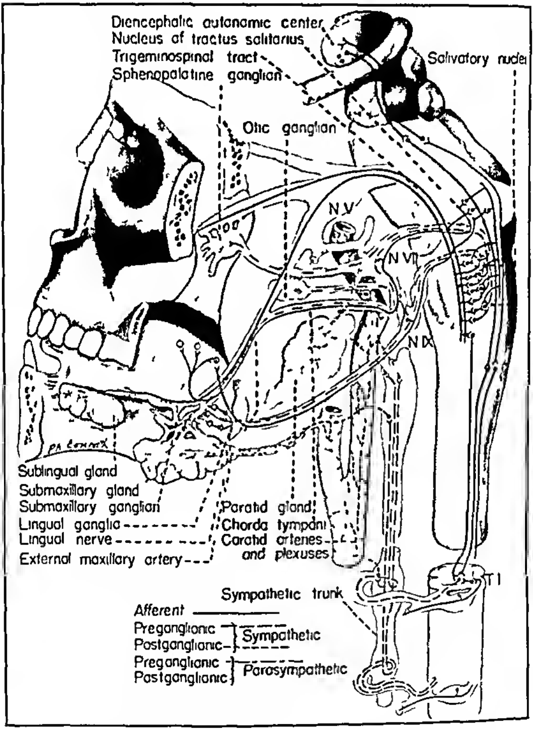


FIG 71 —Diagrammatic illustration of the innervation of the salivary glands

Parasympathetic fibers reach the parotid gland from the otic ganglion through the auriculo-temporal nerve The parasympathetic innervation of the submaxillary and sublingual glands is derived from the submaxillary

ganglion and ganglion cells located within the hilum of the submaxillary gland The nerve fibers reach the glands through direct rami and via the lingual nerve Sympathetic fibers reach the parotid gland via the internal carotid plexus, the submaxillary and sublingual glands via the external carotid plexus and the plexus on the external maxillary artery

The postganglionic fibers which supply the salivary glands are mainly unmyelinated and of small caliber Most of them lie in close proximity to the ducts along which they may be traced into the lobules of the gland where they form plexuses on the intralobular ducts Slender strands of fibers may be traced from these plexuses onto the alveoli where they form perialveolar plexuses (Huber, 1896) According to Dogiel (1893), Berkeley (1893) and Huber (1896), some nerve fibers penetrate the membrana propria and terminate in direct relation to the gland cells According to Sasybin (1933), the fibers which penetrate the membrana propria form a plexus between it and the gland cells, from which arise offsets which end in terminal enlargements in relation to the gland cells This plexus, which includes both parasympathetic and sympathetic fibers is more abundant in the parotid gland than in the submaxillary and the sublingual

Functional Regulation of the Salivary Glands —The parotid submaxillary and sublingual glands exhibit secretory activity mainly while food is being eaten and in response to reflex and psychic stimulation In the ruminants the parotid gland exhibits some secretory activity even in the absence of food in the mouth and while the animal is at rest In the sheep, according to Scheunert and Trautmann (1921), the parotid gland produces a continuous flow of saliva but the submaxillary gland exhibits secretory activity only while the animal is feeding They observed no secretory output from the submaxillary gland in this animal during the intervals between feeding even while cud chewing was in progress Scheunert, Krzywanek and Zimmermann (1930) found no evidence of psychic stimulation of the parotid gland in the sheep and the cow but movements of the lips, tongue and jaws by the hungry animals in the presence of food elicit reflex secretory activity of this gland Cud chewing also acts as a strong stimulus to parotid activity on the chewing side whereas the parotid on the opposite side is not appreciably stimulated by this process Eating of hay commonly elicits parotid activity on the chewing side whereas eating of oats or turnips elicits parotid activity on both sides This stimulation is essentially mechanical Chemical stimulation of salivary secretion probably is unimportant in the ruminants The continuous secretion of the parotid in these animals probably is correlated with the functional activity of the ruminant stomach In the dog the parotid gland does not react to sympathetic stimulation by increased secretory activity The parotid gland cells however, exhibit characteristic histologic changes following a period of sympathetic stimulation (Hitzker 1914) The secretory activity of the submaxillary and sublingual glands is augmented both by parasympathetic and sympathetic stimulation

Specific Effects of Nerve Stimulation —The secretory effects on the salivary glands of stimulating their parasympathetic and sympathetic nerves respectively differ somewhat in different animals In the dog, according to the results of Heidenhain s (1878) classical experiments the submaxillary and sublingual glands begin to secrete promptly when the chorda tympani is stimulated by weak induction shocks By proper regula-

tion of the stimulation this secretory activity may be kept up for hours. The secretion produced under these conditions is thin and watery and contains a very low percentage of solid matter. The flow of blood through the gland is increased and the organ assumes a redder color. The veins also are distended. If they are cut, the blood flows out rapidly and is redder than the blood in the resting gland. These facts indicate dilatation of the small arteries and suggest that the parasympathetic nerves in question also contain vasodilator fibers. Stimulation of the sympathetic nerves supplying these glands brings about quite a different result. The meager secretion produced is thick and turbid and contains a high percentage of total solids. The gland also becomes pale. The veins are not distended. If they are cut the blood flows out less rapidly and is darker than in the resting gland. These facts show that sympathetic stimulation also brings about vasoconstriction in the glands.

The abundant flow and watery character of the salivary secretion produced during parasympathetic stimulation undoubtedly is determined at least in part by the increased blood supply to the glands. On the other hand, the meager flow and thick character of the secretion produced during sympathetic stimulation is correlated with a diminution in the blood supply due to vasoconstriction. These facts might suggest that the effects of nerve stimulation on salivary secretion are mainly manifestations of vasomotor phenomena, the rate of secretory activity depending only on the volume and pressure of the blood flowing through the glands. By the use of a mercury manometer Ludwig (1851) demonstrated that stimulation of the chorda tympani for a certain length of time may result in secretory pressure in the submaxillary gland which greatly exceeds the intraglandular blood pressure. This shows that filtration from the blood is not the only factor involved in the secretory activity of the salivary glands. If the flow of blood be shut off completely from the submaxillary gland, stimulation of the chorda tympani still results in secretory activity for a short time. Following the injection of atropine into the submaxillary gland, stimulation of the chorda tympani also results in vasodilatation but no secretory activity. This suggests the existence in the chorda tympani of vasodilator and secretory fibers and that atropine paralyzes the latter but not the former. Beznak (1933) also reported experimental data in support of the hypothesis that the chorda tympani includes vasodilator and secretory fibers to the salivary glands and pointed out that, with properly graded stimulation of the chorda tympani, salivary secretion and vasodilatation may be elicited independently of one another.

Simultaneous weak stimulation of the chorda tympani and the cervical sympathetic trunk brings about a greater increase in salivary secretion than the stimulation of either nerve separately (Langley, 1878). Simultaneous stimulation of these nerves by means of a strong stimulus, however, results in a lesser increase in secretion than stimulation of the chorda tympani alone (Czermak, 1857). This might be explained on the assumption that the sympathetic nerves under certain conditions exert an inhibitory influence on the salivary glands. That sympathetic stimulation may inhibit secretory activity of the submaxillary gland brought about by stimulation of the chorda tympani was observed by Czermak (1857). Mislawsky and Smirnow (1893) observed a similar inhibitory effect of sympathetic stimulation on the secretory activity of the parotid gland.

brought about by stimulation of the auriculotemporal nerve That vasoconstriction due to sympathetic stimulation played an important role in these results seems highly probable On the other hand, Langley (1889) has shown that the secretory effect of sympathetic stimulation on the submaxillary gland is heightened by preceding stimulation of the chorda tympani for a short time This result led him to conclude that parasympathetic stimulation increases the irritability of the gland cells It also favors the assumption that the sympathetic nerves include true secretory fibers to the salivary glands According to Holzlohner and Airapetianz (1933) heightening of the effect of sympathetic stimulation on the submaxillary gland by preceding stimulation of the chorda tympani does not occur if the chorda stimulation has been preceded by sympathetic stimulation On the contrary, sympathetic stimulation may fail to elicit any secretory activity under these conditions According to Stavraky (1931) the augmenting effect of sympathetic stimulation on the secretory output of the submaxillary gland in the dog particularly after stimulation of the chorda tympani, is in part a mechanical phenomenon due to contraction of the gland According to his findings, this gland contains certain contractile elements the nature of which as yet is unknown, which are activated by stimulation of certain of the fibers in the sympathetic supply In addition to these fibers, the sympathetic supply to the submaxillary and sublingual glands also includes secretory and vasomotor fibers

Knowledge of the specific distribution of the sympathetic and parasympathetic fibers, particularly in the submaxillary gland and the specific changes brought about in the gland cells by sympathetic and parasympathetic stimulation respectively was advanced materially by the experimental histologic studies of Hitzker (1914) According to his findings the histologic changes in the mucous cells brought about by stimulation of the chorda tympani and the cervical sympathetic are similar in character and indicate heightened secretory activity On the other hand, the histologic changes brought about in the serous cells are dissimilar The effect on these cells of stimulation of the chorda tympani is manifested by enlargement and increased granulation of their cytoplasm The effect of sympathetic stimulation is manifested by diminution in the size of these cells, decreased granulation of their cytoplasm and a less intense staining reaction of the nucleus Simultaneous stimulation of the chorda tympani and the cervical sympathetic according to Hitzker, results in summation of the effects of both nerves on the mucous cells but in interference of the sympathetic and parasympathetic influences with each other on the serous cells resulting in enlargement of the cells due to parasympathetic, and decreased granulation of their cytoplasm due to sympathetic stimulation, and no change in the staining reaction of the nucleus These facts strongly suggest that both the mucous and serous cells are innervated by both parasympathetic and sympathetic fibers Although the effect on the mucous cells of stimulation of the chorda tympani for a given interval is more marked than that of stimulation of the cervical *sympathetic* for an equal interval the impulses conducted to these cells by parasympathetic and sympathetic fibers respectively must affect them in essentially the same manner The effect of the parasympathetic and sympathetic fibers respectively on the serous cells must be regarded as antagonistic These facts seem to warrant the conclusion that the impulses conducted to the

salivary glands by the parasympathetic and sympathetic fibers respectively differ qualitatively in their effect, particularly on the serous cells. Furthe more, the results of Babkin's (1913) experiments involving extirpation o the superior cervical sympathetic ganglion also suggest that impulses con ducted to the salivary glands by the same fibers may differ qualitatively in their effect on the gland cells. Vasomotor changes in the salivary glands effected by the nerves in question, nevertheless, must always play an important role in determining the volume and character of the secretion produced.

In a quantitative study of the protein content of the saliva secreted by the submaxillary gland due to varied stimulation of the chorda tympani Langstroth, McRae and Stavraky (1938) found that the secretion of protein involves a chemical reaction which transforms granular material within the gland cells to a state in which it is readily carried out by the flow of water. They also found that the secretion of protein, the secretion of water and the regulation of cell membrane permeability are dependent on the rate at which some activating substance is liberated within the gland due to the stimulation. In a spectroscopic study of the composition of the secretion of the submaxillary gland in the cat, due to stimulation of the chorda tympani, sympathetic stimulation and the administration of adrenin they found that the saliva secreted during stimulation of the chorda tympani differs widely from that secreted during stimulation of th ta that secreted due to the administration of adrenin is similar to that secreted during sympathetic stimulation. The saliva secreted during sympathetic stimulation but not identical with it administration of adrenin also differs from that secreted during chorda tympani stimulation before the administration of adrenin.

In experiments carried out on animals which had been subjected to unilateral cervical sympathectomy, Walser (1934) observed greater heat production in the normally innervated salivary glands than in those on the sympathectomized side, although the vessels in the sympathectomized glands were dilated. He concluded that the greater heat production in the normally innervated glands is due to sympathetic nerve impulses and that sympathin plays a role in heat production.

Henderson and Roepke (1933) reported certain data which they interpreted as indicating the presence of acetylcholine in the saliva secreted by the submaxillary gland during stimulation of the chorda tympani. Secker (1934–1936) reported experimental data which indicate the presence of a depressor substance in the secretion of the submaxillary gland in the cat during sympathetic stimulation. He at first regarded this substance as acetylcholine but later concluded that it is not identical with the latter substance. Feldberg and Guimarais (1935), confirmed the occurrence of a depressor substance in the cat's saliva during sympathetic stimulation but pointed out that it is not identical with acetylcholine and that the sympathetic nerves which supply the salivary glands are in no sense cholinergic. Experimental data reported by Gibbs (1935) also fail to support the assumption that the depressor substance in saliva is acetylcholine.

Reflex Salivary Secretion.—The salivary glands react reflexly both to stimulation of the oral mucosa and strong stimulation of afferent nerves from other parts of the body, particularly the eyes, ears, and nasal mucosa

In general, the mere presence of water at ordinary temperatures or inert substances e g, pebbles, in the mouth does not call forth a flow of saliva but the salivary glands react more or less specifically to mechanical, chemical and thermal stimulation of the oral mucosa On the basis of experimental studies, Heymann (1904) concluded that the oral mucosa includes receptors which possess a high degree of specificity and that those which receive certain types of stimuli are not uniformly distributed The reflex response of the salivary glands, therefore, varies with the kind of stimulation and the area of the oral mucosa involved This probably is an important factor in determining the quantitative and qualitative variations in the salivary secretion while different kinds of food are being eaten

Strong afferent stimulation of a somatic nerve e g, the sciatic, results not only in an increased output of saliva but also in an increase in the organic constituents of the salivary secretion Section of the cervical sympathetic trunk does not abolish reflex salivary secretion but results in qualitative changes in the saliva produced on the side of the operation Section of the chorda tympani abolishes reflex activity of the submaxillary and sublingual glands

Paralytic Salivary Secretion —Certain of the earlier investigators, including Bernard (1864), Heidenhain (1868), Langley (1885) and Bradford (1888), supported the theory that the submaxillary gland exhibits continuous secretory activity for two weeks or longer following section of the chorda tympani Sympathetic stimulation during this so called paralytic secretory activity, according to their observations, resulted in increased secretion but section of the cervical sympathetic had no effect on it According to Langley dyspnea augments and apnea inhibits paralytic salivary secretion This led him (Langley, 1898) to conclude that the gland cells which have become hyperirritable due to deprivation of their parasympathetic innervation react to the presence of carbon dioxide in the blood by paralytic secretory activity The fact that such secretory activity usually ceases within three weeks after section of the nerve militates against this conclusion Unilateral section of the chorda tympani also is followed by increased secretion of the submaxillary gland of the opposite side This was first observed by Heidenhain in the dog and later corroborated by Langley (1885) in the cat As observed by Heidenhain, section of the nerve has no effect on this so-called antiparalytic salivary secretion consequently, this phenomenon cannot be associated with hyperirritability of the salivary center as suggested by Langley, but its real cause remains to be discovered

In experiments reported by Seo (1934) the submaxillary glands in dogs failed to exhibit continuous secretory activity following section of the chorda tympani and the lingual nerve and extirpation of the superior cervical sympathetic ganglion He observed some secretory activity of the glands associated with feeding, which he regarded as a conditioned response to the giving of food, consequently, he interpreted his findings as opposed to the theory of paralytic secretion Inasmuch as secretory activity associated with feeding was not abolished by the operative procedures referred to however, his findings do not afford conclusive evidence that the submaxillary gland cannot secrete in the absence of nerve impulses

In experiments on cats reported by Fleming and Macintosh (1935), the secretory response of the submaxillary gland to sympathetic stimulation

was greatly increased following degeneration of the chorda tympani They interpreted this result as indicating true heightened irritability of the secretory cells to sympathetic stimulation

Effects of Drugs on Salivary Secretion —Intravenous injection of adrenin brings about a marked increase in the production of saliva in the cat (Langley, 1901, 1902) The effect of adrenin on salivary secretion is less marked in the dog and rabbit and absent in man (Bauer, 1912) Pilocarpine, acetylcholine, acetyl beta-methylcholine chloride and other parasympathomimetic substances also elicit increased salivary secretory activity Atropine in moderate doses abolishes the influence of the parasympathetic but not of the sympathetic nerves on salivary secretion Ergotoxine abolishes the effect of the sympathetic but not that of the parasympathetic nerves on the submaxillary gland (Dale, 1906)

Following unilateral degeneration of the chorda tympani in the cat pilocarpine and acetylcholine stimulate the normally innervated submaxillary gland more strongly than the paralytic one (Fleming and Macintosh 1935) Pierce and Gregersen (1937) reported increased sensitivity of the submaxillary gland in the dog to pilocarpine a few days after section of the chorda tympani The apparent discrepancy between the results obtained in these two series of experiments probably can be explained on the basis of the difference in the time intervals following section of the chorda tympani

Innervation of the Teeth —The teeth are abundantly innervated through afferent nerve fibers which are mainly components of the alveolar rami of the trigeminal nerves The distribution of the afferent fibers in the dental pulp has been described by various investigators including Lewinsky and Stewart (1935 1938) Berkelbach van der Sprenkel (1936) Brashear (1937) and Tiegs (1938) These fibers form an abundant plexiform structure in relation to the odontoblasts and, according to some of the accounts some nerve fibers terminate in relation to the distal processes of odontoblasts which traverse the dentinal canals If the odontoblasts may be regarded as receptive cells this arrangement would readily explain the sensitivity of the dentine Afferent nerve fibers also supply the peridental membrane

The occurrence of sympathetic nerve fibers in the dental pulp and the peridental membrane has been amply demonstrated (Berkelbach van der Sprenkel, 1936 Wasserman 1939, Bradlaw 1939, Christensen 1940) According to Christensen's account, sympathetic nerve fibers join the alveolar nerves via the plexus on the external carotid artery and its branches As determined by degeneration experiments relatively few sympathetic fibers actually enter the dental pulp Within the pulp most of these remain closely associated with the blood vessels Sympathetic fibers also enter the peridental membrane along the blood vessels These fibers probably are distributed mainly to the vascular musculature

Innervation of the Hypophysis —The hypophysis is innervated through nerve fibers which are abundantly distributed throughout the posterior lobe and less abundantly throughout the anterior lobe The numbers of fibers in the posterior lobe bear no direct relationship to the degree of vascularity of the part in question (Croll, 1928) Most of these fibers are derived directly from the supraoptic and paraventricular hypothalamic nuclei the floor of the third ventricle and the lateral regions of the tuber cinereum (Pines 1925, Greving 1925, Stengel, 1926, Cushing 1930 Fisher *et al*, 1935) Sympathetic fibers derived from the carotic plexuses,

mainly via the cavernous plexus, may be traced into the capsule of the hypophysis particularly on the upper surface of the anterior lobe (Rasmussen, 1938) Many of these fibers enter the gland along blood vessels and some of them apparently terminate in relation to gland cells (Berkley, 1894, Dandy, 1913, Pines, 1925,, Croll, 1928, Hair, 1938) Fibers arising from cephalic parasympathetic ganglia probably play no part in the innervation of the hypophysis (Hair and Mezen, 1939)

In an intensive study based on preparations of human material, Rasmussen (1938) found that not fewer than 50,000 unmyelinated nerve fibers of small caliber extend from the hypothalamus into the infundibulum Most of these appear to be distributed to the posterior lobe, and relatively few enter the anterior lobe through the pars intermedia The number of those which penetrate into the anterior lobe is regarded by Rasmussen as negligible

As the sympathetic fibers derived from the cavernous plexus approach the hypophysis according to Rasmussen they form a bundle along either lateral aspect of the infundibular stalk Many of them penetrate deeply into the anterior lobe where some become associated with blood vessels and some ramify among the gland cells Strands of fibers which deviate from the bundles along the infundibulum extend downward and forward in the capsule From these strands, fibers enter the substance of the anterior lobe in small numbers at many points Some of these fibers also ramify among gland cells but relatively large portions of the anterior lobe appear to be devoid of nerve fibers

Regulation of Hypophyseal Functions —Much of the secretory activity of the hypophysis is regulated through hormonal agents and probably is independent of nerve impulses Data bearing directly on the influence of nerve impulses in hypophyseal functions are meager but certain data indicate clearly that some hypophyseal functions are subject to regulatory influences exerted through hypothalamico-hypophyseal fibers and some through the sympathetic innervation of the gland

The influence on the production of the antidiuretic hormone in the posterior hypophyseal lobe of nerve impulses emanating from the hypothalamus through the hypothalamico-hypophyseal tract and the effect of interruption of this tract on water and fat metabolism are discussed in Chapter IV The release of gonadotropic hormone from the anterior hypophyseal lobe in response to electrical stimulation of the hypothalamus also has been demonstrated (Marshall and Verney, 1936 Harris, 1937, Haterius 1938) Section of the infundibulum results in immediate disturbance of various anterior lobe functions in some degree Fisher, Ingram and Ranson (1938) reported that female cats with small hypothalamic lesions which interrupted the hypothalamico hypophyseal tract, thus causing diabetes insipidus, were never observed to come into heat and did not breed in the laboratory Disturbances of the reproductive functions associated with damage to the hypothalamico-hypophyseal tract particularly in female guinea pigs have been reported in greater detail by Dey Fisher, Berry and Ranson (1940)

In experiments on rabbits, reported by Brooks (1938), ovulation, which normally occurs only after coitus in these animals was abolished by transection of the infundibulum In experiments on guinea pigs, in which ovulation occurs spontaneously, as reported by Dempsey (1939), this

function was not disturbed by transection of the infundibulum. Ovulation, mating, pregnancy, parturition and lactation in rats with the infundibular stalk interrupted also have been reported (Uotila, 1939).

In view of these and other experimental data, it may be assumed that the integrity of the hypothalamico-hypophyseal tract is not essential for the normal functioning of the anterior hypophyseal lobe in animals living under ordinary conditions. The gonadotropic, thyrotropic, adrenocorticotropic, growth and probably lactotropic hormones apparently may be secreted in sufficient quantity, in the absence of nerve impulses emanating from the hypothalamus, to supply the normal requirements of the respective end-organs. The functional rhythm of the anterior lobe, however, may be modified in certain environmental situations by nerve impulses which reach the hypophysis through the hypothalamico-hypophyseal tract.

The seasonal reproductive activities of various species of birds and mammals have occupied the attention of not a few investigators particularly during the past decade. The accumulated data seem to support the assumption that the resumption of gonadal activity in the spring in these species is associated with the increasing daily illumination (Ringoen and Kirschbaum, 1937, 1939; Riley, 1937, and others). Light obviously is a stimulating factor in the production of the gonadotropic anterior hypophyseal hormone. According to Scharrer (1937), light impulses which reach the hypothalamus may affect the entire autonomic system and thus play a role in the day-night rhythm. Through the hypothalamico-hypophyseal tract they exert a stimulating influence on various hypophyseal functions, particularly the production of the gonadotropic hormone, thus effecting increased gonadal activity.

The effect of hypothalamic impulses in the regulation of body temperature seems to be exerted in part through the hypothalamico-hypophyseal tract. In experiments on dogs reported by Hemingway, Rasmussen, Rasmussen and Wikoff (1940), transection of the infundibulum resulted in a persistent hyperthermia, the body temperature being elevated 0.5 to 1.0 degree above the normal level. The operated animals reacted normally to cold but, due to their continuous elevated temperatures, the threshold temperatures for shivering and peripheral vasoconstriction were elevated to the same degree as body temperature. They were somewhat hypersensitive to heat, as indicated by the measured diathermy heat required to cause panting and peripheral vasodilatation and the casual observation that they panted more frequently than normal dogs.

The sympathetic nerves probably exert no direct influence on hypophyseal functions except in the anterior lobe. In experiments on rabbits reported by Friedgood and Pincus (1935), the rate of production of the gonadotropic hormone was increased by faradic stimulation of the sympathetic nerves to the hypophysis. This observation supports the assumption that the sympathetic nerves may be responsible at least in part for the stimulation of the anterior hypophyseal lobe during coitus which in the female rabbit results in the release of its gonadotropic hormone in increased amounts.

CHAPTER XVII

SYMPATHETIC NERVES IN RELATION TO SKELETAL MUSCLE

Anatomic Data.—The cerebrospinal nerves through which the skeletal muscles are innervated are traversed by numerous sympathetic nerve fibers which innervate blood vessels and other peripheral tissues. Many sympathetic nerve fibers, consequently, lie in proximity to skeletal muscle fibers. Certain recorded observations also support the assumption that sympathetic nerve fibers actually effect functional connections with skeletal muscle fibers. Among the early investigators who described nerve fibers morphologically similar to sympathetic fibers in skeletal muscles may be mentioned Tschiriew (1879), Bremer (1882), Huber and De Witt (1897, 1900), Ruffini (1900), Dogiel (1902), Perroncito (1901, 1902), Gemelli (1905) and Botezat (1906). The most significant anatomic data in support of the view that the skeletal muscles are innervated through sympathetic fibers have been advanced by Boeke and his associates. As early as 1909 Boeke recognized the existence in skeletal muscles of a system of fine unmyelinated nerve fibers which appeared to be quite independent of the cerebrospinal nerve fibers. In a series of later papers (1911–1913) he discussed this "accessory" system more fully and advanced the opinion that its constituent fibers belong to the autonomic nervous system.

In order to determine the origin of the fibers in question more accurately, he attacked the problem by experimental methods. In one series of experiments (1916, 1917) one or another of the nerves supplying the extrinsic muscles of the eye was resected close to its origin from the brain. Three to five days were allowed for the degeneration of the divided fibers. The animal was then killed and the ocular muscles prepared for study according to the Bielschowsky method. A careful study of these preparations showed that the medullated nerve fibers and their terminal structures were undergoing degeneration, but the unmyelinated "accessory" fibers with their hypolemmal endings on the muscle fibers remained intact. Sections of the extrinsic ocular muscles prepared after degeneration of the sympathetic fibers following extirpation of the superior cervical sympathetic ganglion also showed intact unmyelinated fibers, but in reduced numbers. Boeke, therefore, concluded that the unmyelinated nerve fibers observed in preparations of the extrinsic eye muscles are autonomic but most of them arise in a cranial autonomic ganglion.

In a further experimental study carried out by Boeke and Dusser de Barenne (1919), both anterior and posterior roots of the sixth to the ninth thoracic nerves inclusive were resected and the corresponding spinal ganglia extirpated. The animals (cat) were killed one month after operation. In order to avoid confusion due to overlapping of the areas of distribution of the intercostal nerves, muscle tissue to be prepared for study was taken from the seventh intercostal space. Preparations of this tissue showed neither intact myelinated nerve fibers nor the motor end-plates associated with them but fine unmyelinated nerve fibers terminating on muscle fibers by means of delicate end rings, end loops or end-nets were

present. In view of the conditions of the experiments, the conclusion that the unmyelinated fibers in question are sympathetic in origin could hardly be avoided.

In a similar experimental investigation, Agduhr (1919) examined preparations of certain of the small muscles of the extremities, particularly the *interossei in the cat following degeneration of the spinal nerve fibers*. His findings in general corroborated the earlier findings of Boeke. Kuntz and Kerper (1924) and Kuntz (1927) also recorded data obtained in experimental studies similar to those of Boeke and Agduhr which they interpreted as indicating the existence of fibers of sympathetic origin with terminal structures on muscle fibers in the intercostal muscles, the muscles of mastication and muscles of the extremities in the dog.

On the basis of a review of his earlier work and further experimental data, including the results of investigations carried out by others, particularly those involving degeneration of the cerebrospinal nerve fibers, Boeke (1927) concluded that the morphologic data available show unmistakably that skeletal muscles are supplied with sympathetic as well as sensory and motor cerebrospinal nerve fibers. Nakanishi (1932) also reported the existence of unmyelinated fibers of sympathetic origin in the muscles of the posterior extremities of the frog after degeneration of the spinal nerve fibers.

The results of certain other histologic studies, particularly those of Kulchitsky (1924), Hunter and Latham (1925), Kure *et al.* (1925), Garven (1925) and Stefanelli (1929), also support the theory that skeletal muscles are supplied with fibers of sympathetic origin, but inasmuch as they are based on preparations of normally innervated muscles they are less convincing than the results of the experimental anatomic studies cited above.

In spite of the volume of anatomic and physiologic data which seem to support the hypothesis that sympathetic nerve fibers effect functional connections with skeletal muscles, this concept has not been universally accepted. Murray (1924) found no evidence which supports it in his study of preparations of the limb muscles of the frog. Langworthy (1924) found no intact nerve fibers except those associated with the blood vessels in preparations of the muscles of the cat's tongue following bilateral section of the hypoglossal nerve. Hinsey (1927) attempted to show that most of the recorded observations which have been interpreted as supporting the theory of the sympathetic innervation of skeletal muscles could be interpreted quite as well in some other way. He suggested that the fine unmyelinated nerve fibers observed in preparations of skeletal muscles following degenerative section of the cerebrospinal nerve fibers may be either unmyelinated branches of sensory or motor fibers which have not undergone degeneration, or regenerating somatic motor fibers. Hines and Tower (1928) found no evidence of the existence of nerve fibers of sympathetic origin which terminate in relation to skeletal muscle fibers. In a more comprehensive study of the innervation of limb muscles in cats, dogs and goats in normal material, sympathetically denervated material and material in which each of the three components of the innervation, *viz.*, the sensory, motor and sympathetic nerve fibers, had been isolated by degenerative section of the other two, using the methylene-blue, Bielschowsky's silver and Ranvier's gold chloride technics, Tower (1931) again found no evidence of sympathetic nerve fiber terminations on skeletal muscle fibers and ad-

vanced certain data which she interpreted as indicating that the nerve fibers which supply the blood vessels and the striated muscle fibers respectively are derived from the intramuscular nerve trunks separately and do not communicate at any point in their peripheral distribution

Wilkinson (1929) reported that he had critically examined some of the original preparations of Boeke and Agduhr *i e*, some of the preparations which represent the principal available histologic evidence of the sympathetic innervation of skeletal muscles, and found them unconvincing With regard to Boeke's findings in preparations of the eye muscles following section of their somatic nerve supply, he maintained that there were certain sources of error which Boeke failed to avoid particularly the short period allowed for the degeneration of the somatic nerve fibers the possible existence of ganglion cells along the nerve trunks distal to the point of section and the existence of fine epilemmal endings of proprioceptive nerve fibers He interpreted the nerve endings in the eye muscles which Boeke described as the terminations of sympathetic or parasympathetic fibers as terminations in the arborizations of proprioceptive sensory fibers The findings of Boeke and Dusser de Barenne in preparations of intercostal muscles in which the spinal nerve fibers had undergone degeneration he asserted cannot be accepted With regard to Agduhr's preparations, which were taken from kittens after allowing five to six days for the degeneration of the somatic nerve fibers he stated that the endings which this investigator regarded as those of fibers of sympathetic origin are normal endings of myelinated somatic motor fibers In another study (1930) in which he avowedly attempted "to repeat the work of Boeke and Agduhr if possible in a more comprehensive manner" he again failed to corroborate the findings of these investigators In still another paper (Wilkinson 1934) which embodies the results of further experimental studies, he again reported only negative findings regarding the existence of a sympathetic innervation of skeletal muscles

Coates and Tiegs (1931) found no sympathetic fibers except those which supply the blood vessels in preparations of muscles of the hind limb of a dog eight and a half days after section of both roots of the lumbar and sacral nerves, leaving the communicating rami intact In preparations of muscles of the fore-limb of a dog taken thirty-eight days after extirpation of the inferior cervical sympathetic ganglion they found no nerve supply to the blood vessels but recognized certain terminal structures which they regarded as identical with those of the accessory fibers of Agduhr and others These they interpreted as the terminations of branches of somatic fibers

The negative findings recorded above regarding the existence of a sympathetic nerve supply to skeletal muscles cannot be disregarded but they neither prove the non-existence of such a nerve supply nor disprove the positive findings of Boeke and others That the Dutch investigators should have fallen into the particular errors attributed to them by Wilkinson seems improbable Boeke (1930) also called attention to the dissimilarity between certain of his published drawings and those of Wilkinson which presumably were made from the same preparations and pointed out that the latter do not illustrate correctly the structures in question and in some instances are misleading In view of Boeke's extensive experience with histologic technic and in the interpretation of histologic preparations,

his criticism of Wilkinson's work does not inspire confidence in the latter's findings

In Boeke's (1933, 1937) later investigations of the innervation of skeletal muscles, he described in minute detail a plexiform structure made up of anastomosing bands of extremely delicate neurofibrillar strands which encircle and envelope the muscle fibers and are so closely applied to them that they appear to be nearly imbedded in the sarcolemma. At some points these strands actually lie in the same planes as the striations of the muscle fibers (Fig. 72). This plexiform structure, as Boeke has pointed out, obviously has not been observed in the preparations studied by any

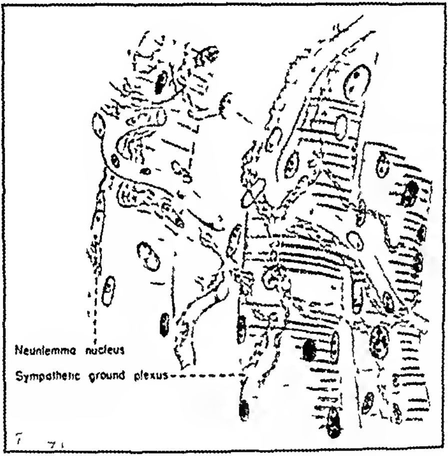


FIG 72 —Redrawn from Boeke (1933) to illustrate his concept of the sympathetic terminal structure in relation to skeletal muscle and its capillary vessels

of the investigators who failed to find evidence of the existence of sympathetic fibers which terminate in relation to skeletal muscle fibers. He also failed to observe it in his own earlier studies. After he had become familiar with its structural characters and staining reactions in material prepared according to improved technical methods, he recognized it at least in some areas in his older preparations. He therefore, expressed the opinion that failure on the part of some investigators to observe fibers of sympathetic origin which terminate in relation to skeletal muscle fibers has been due at least in part to faulty technic; consequently, their negative findings can have little weight as compared with the positive findings reported by himself and others

The existence in the muscles of the tongue (Imagawa 1927) and face (Sakurasawa, 1927) and the extrinsic muscles of the eye (Suniga, 1927) of parasympathetic fibers has been maintained on the basis of histologic changes observed in these muscles following parasympathectomy Kure *et al* (1928, 1930) advanced data which they interpreted as indicating the existence of efferent fibers in the dorsal roots of the spinal nerves On the basis of these findings and the histologic changes which they claim to have observed in muscles of the hind limbs following section of the dorsal roots of the lumbar nerves or removal of the spinal ganglia, Kuré and his associates have advanced the opinion that the muscles of the extremities also are innervated through parasympathetic nerves In view of the negative results obtained in repeated attempts to demonstrate the existence of efferent fibers in the dorsal spinal nerve roots this point of view cannot be supported

Physiologic Data — Sympathetic Nerves and Muscle Tonus — *General Experimental Data* — The earliest investigators who undertook to study the effects of sympathetic nerve impulses on skeletal muscles by the use of physiologic and experimental methods quite naturally surmised that any influence exerted on skeletal muscles through the sympathetic nerves must affect muscle tonus On the basis of experimental studies carried out mainly on frogs de Boer (1913) advanced the theory that the tonus of skeletal muscles is mediated solely through the sympathetic nerves Although this theory obviously is erroneous the experimental findings reported by de Boer focussed attention on the sympathetic nerves as a possible factor in the regulation of muscle tonus

Langelaan (1915) advanced the theory that muscle tonus comprises a 'contractile component concerned with movement and the assumption of posture, and a 'plastic' component concerned with the maintenance of assumed posture, the former being mediated through the cerebrospinal, the latter through the sympathetic nerves On the basis of an extensive series of experiments carried out on frogs, he (1922) concluded that muscles deprived of their sympathetic innervation lose much of their plasticity, the effect of which is most apparent in the attitudes of the animal In a later paper (Langelaan 1931) he reported permanent hypotonus of the muscles of the corresponding hind limb of a cat two years after unilateral extirpation of the lumbar segments of the sympathetic trunk, which he regarded as due to the loss of the plastic component Experimental data reported by Lopez and von Brucke (1916), Dusser de Barenne (1916), Salek and Weitbrecht (1920) and Maumary (1922) also support the assumption that sympathetic denervation results in diminution of tonus in the skeletal muscle in the area affected The concept of contractile and plastic tonus as distinct components mediated through separate systems of nerve fibers although not supported by the results of later investigations played an important role in many of the subsequent discussions of muscle tonus as related to the sympathetic nerves

In contrast to the observations cited above, many investigators, including Cobb (1918) Takahashi (1922) Newton (1924), Coman (1926), Tower (1926), Tower and Hines (1929), Bisgard (1931) and others using various mammals as the experimental animals have failed, by direct methods of observation to detect even a temporary diminution in the tonus of the corresponding limb muscles following sympathetic denervation On the

other hand Fulton (1928) reported well marked diminution of tonus in the muscles of the lower extremity in a patient following lumbar sympathectomy. McCullagh, McFadden and Milroy (1930) also reported appreciable diminution of tonus in the corresponding quadriceps femoris muscle in the dog following unilateral lumbar sympathectomy.

In experimental studies on cats and dogs, Kuntz and Kerper (1926) failed except possibly in a few cases, following sympathetic denervation of a limb, to detect a diminution of tonus in the muscles of that limb by direct observation or palpation of the muscles while the animal was in the waking state. When the animal was subjected to surgical anesthesia the muscles of the limb deprived of its sympathetic innervation became more flaccid than those of the other limbs. When the animal, under deep anesthesia, rested on its back in a symmetrical position so that the force of gravity acted equally on the limbs on both sides and postural reflexes due to an asymmetrical position of the head and neck were obviated, the limb deprived of its sympathetic innervation almost invariably dropped to a lower position than the one on the opposite side. In the case of either the fore or hind limbs, the difference in the posture of the limb deprived of its sympathetic innervation and the one on the opposite side was sufficiently well marked, under these conditions, to be easily observed. The phenomenon could be demonstrated in all but a few animals in a relatively large series. Coates and Tiegs (1928) failed to corroborate these findings in a series of five dogs.

On the basis of a series of experiments carried out on birds (fowls and sea gulls), Hunter (1924) reported that the adducted position characteristic of the wing at rest is no longer fully maintained following section of the sympathetic trunk immediately caudal to the roots of the nerves which make up the brachial plexus. He interpreted this result as indicating that the plastic tonus of the wing muscles is mediated through their sympathetic innervation. Following section of the dorsal roots of the lower four cervical nerves, he found that the wing exhibited a tendency to remain in any position in which it was passively placed. This he regarded as due to the plastic component of tonus mediated through the sympathetic nerves. Following section of the sympathetic trunk just below the brachial plexus, and the dorsal roots of the lower four cervical nerves, he found that the wing tended to hang dependent. This he regarded as due mainly to the loss of plastic tonus. Hunter interpreted these findings as proving conclusively that the plastic tonus of the wing muscles is mediated through their sympathetic innervation.

In a series of experiments carried out on fowls and pigeons Kuntz and Kerper (1925) corroborated most of the observations of Hunter cited above. Section of the sympathetic trunk just below the brachial plexus did not result in appreciable drooping of the wing in all cases, particularly if the operation was carried out with minimum traumatic injury to the nerves of the brachial plexus. Coates and Tiegs (1928) also reported that section of the sympathetic trunk below the brachial plexus, in their experiments, did not result in appreciable drooping of the wing when the proper operative precautions were observed. Tiegs (1931) reported that division of the preganglionic fibers supplying the wing of the pigeon did not result in drooping of the wing even when the possibility of reflex compensation by somatic nerves was eliminated by section of the dorsal roots of the

nerves of the brachial plexus According to Van Dijk (1930), section of the sympathetic trunk or the dorsal root of the first thoracic nerve in the pigeon, results in abduction of the wing and lowering of its tip, particularly after exercise He (1932) also reported a marked difference in the tonic state of the muscles of the bird's wing following section only of its afferent nerve supply and following sympathetic denervation in addition to section of the afferent nerve fibers In the former condition, the wing, when supported in a folded and high position, according to his account, remains in that position when the support is withdrawn, in the latter, it assumes a more dependent posture when the support is withdrawn

We do not now regard the tendency of the wing to remain in whatever position it is passively placed, following section of the dorsal roots of the nerves of the brachial plexus as due to a component of tonus which is mediated through the sympathetic nerves but rather as the result of the loss of the sense of position of the wing due to interruption of the proprioceptive fibers in the dorsal nerve roots The muscles of the deafferented wing are not atonic If the wing is drawn down to the fully dependent position and somewhat away from the bird's body, it does not remain in that position when released but recoils to the bird's side It also is subject to voluntary control and may at any time be replaced voluntarily into its normal position

Popa and Popa (1931) advanced anatomic evidence of the existence of preganglionic fibers in the cervical nerves in the pigeon and corresponding ganglion cell groups in the cervical sympathetic trunk In the light of these findings they cut the communicating rami of the lower four cervical and the first thoracic nerves in order to deprive the wing completely of its sympathetic innervation When this operation was carried out on one side, with minimum traumatic injury to the nerves of the brachial plexus and the same operation, without section of the communicating rami was carried out on the opposite side the wing on the sympathectomized side drooped whereas the other maintained its normal position The drooping of the sympathectomized wing remained constant for thirty five months in one bird and at least twelve months in another

The apparent reduction in the tonus of the resting wing muscles in these instances cannot be explained as the result of injury to the nerves of the brachial plexus since care was taken to avoid injury to these nerves and the corresponding nerves on the opposite side were treated in the same manner except that their communicating rami were not divided Any slight injury which might have been suffered by these nerves, furthermore would have been fully repaired long before the close of the long periods reported during which the resting wings maintained the drooping positions

The discovery by Popa and Popa of preganglionic fibers in the cervical nerves in the pigeon must be regarded as highly significant since it affords an anatomic basis for the explanation of the discrepancies in the results of the experiments referred to above in which attempts were made to deprive the bird's wing of its sympathetic innervation In the light of this discovery, it is evident that the wing was not wholly deprived of its sympathetic innervation in most of the experiments in question The results of these experiments, therefore in as far as they have any bearing on the problem of muscle tonus can have but little value

Ducceschi (1922 1925) reported marked diminution of the postural

tonus of the external ear in rabbits, following extirpation of the superior cervical sympathetic ganglion but pointed out clearly that a difference in the posture of the two external ears, following unilateral extirpation of the superior cervical sympathetic ganglion, usually cannot be observed unless the animal is at rest or feeding in an undisturbed condition. He also observed that the external auditory meatus has a somewhat greater diameter on the side of the operation than on the opposite side while the animal is at rest. Hintze and Seager (1929) observed temporary drooping of the rabbit's ear following cervical sympathectomy, but concluded that the sympathetic nerves normally play no part in the tonus of the external ear muscles.

Fridman (1931) reported the results of a large series of experiments in which sympathetic stimulation resulted in increasing muscle tonus in most cases. In experiments reported by Spychala (1932), sympathetic stimulation resulted in strengthening the quadriceps reflex in dogs with the spinal cord transected at the tenth thoracic level. Pressure on the carotid sinus in intact animals, in his experiments, resulted in weakening the quadriceps reflex. In experiments reported by Mies (1933), stimulation of the aortic and carotid sinus nerves in rabbits resulted in diminution of muscle tonus and section of these nerves resulted in increasing muscle tonus. The former effect was regarded as brought about through lowering of the sympathetic tonus due to stimulation of the aortic and carotid sinus nerves, the latter, through increased sympathetic tonus due to the absence of impulses from the aorta and carotid sinuses. These results were not obtained when the animals were anesthetized with urethane.

Experiments Involving Decerebrate Rigidity.—The characteristic posture of the limbs of an animal in a state of decerebrate rigidity is well known. It has been assumed by some that if muscle tonus is mediated solely or in part through the sympathetic nerves, sympathetic denervation of a limb either would prevent the onset of decerebrate rigidity in that limb or bring about a diminution in the degree of rigidity exhibited by the extensor muscles.

Dusser de Barenne (1916) reported a lesser degree of extensor tonus during decerebrate rigidity, in the limb deprived of its sympathetic innervation in some but not in all cases. Van Rijnberk (1917) and Cobb (1918) failed to observe any effect of sympathetic extirpation on decerebrate rigidity. Royle (1924) reported diminished extensor tonus during decerebrate rigidity in the affected limb, following unilateral lumbar sympathectomy, as a fairly constant result in his experiments on goats. Kanavel, Pollock and Davis (1924), Meek and Crawford (1925), Huggett and Mellanby, (1925) Ranson and Hinsey (1926), Coman (1926), Tower (1926), Forbes *et al.* (1926) and Tower and Hines (1929) reported the results of decerebration experiments in which they could detect no significant effect of sympathetic denervation of a limb on the extensor tonus in that limb during decerebrate rigidity. On the contrary, Coombs and Tulgan (1925) reported that in their decerebration experiments following extirpation of both stellate ganglia, "the rigidity of the fore limbs was very much diminished while the rigidity of the hind limbs persisted unchanged." Van Dijk (1933) reported that, following unilateral extirpation of the stellate ganglion and deafferentation of the fore limb, in decerebrate cats, the muscles of that limb are definitely less plastic than those of the opposite limb, as

indicated by positions and movements passively imposed on both fore limbs or during periods of heightened rigidity

In order to repeat Royle's experiments as nearly as possible Mortensen, Friedbacher and Quade (1928) carried out decerebration experiments in a series of goats, following unilateral lumbar sympathectomy Like the majority of the investigators who used other mammals, they could demonstrate no constant effect of sympathectomy on the extensor tonus in the corresponding limb during decerebrate rigidity Occasionally, they observed differences in the extensor tonus of the two hind limbs while the animal was in a certain position but found that by changing the position the difference in tonus disappeared In a series of experiments carried out on decerebrate cats following unilateral extirpation of the lumbar sympathetic trunk Phillips (1931) observed certain differences in postural tonus and reflexes in the two hind limbs According to his account, the posterior part of the body could be supported at the normal standing height by the limb on the unoperated side but not by the one on the side of the operation Passive flexing force which was sufficient to elicit the lengthening reaction on the sympathectomized side produced a myotatic contracture on the opposite side due to the stretch reflex The lengthening reaction could be elicited on the unoperated side only by increasing the passive flexing force The crossed extension reflex could be elicited on the unoperated side by a weaker stimulus (less stretch) than on the sympathectomized side The amplitude of the crossed extension reflex response also was greater on the normal than on the sympathectomized side The myotatic contraction following the knee-jerk also appeared earlier during relaxation on the sympathectomized than on the opposite side These results, according to Phillips, could be explained on the assumption that the excitability of the receptor ending in the muscles is increased following sympathectomy or on the basis of changes in the circulation

The results of the decerebration experiments cited above show clearly that the exaggerated extensor tonus of decerebrate rigidity is not mediated through the sympathetic nerves but they do not disprove the theory that the sympathetic nerves play a role in the maintenance of normal muscle tonus They afford no positive evidence of real value bearing on the possible functional significance of the sympathetic nerves in relation to skeletal muscles As is well known decerebrate rigidity follows destruction or impairment of the rubrospinal system The exaggerated extensor tonus characteristic of this condition depends mainly on efferent impulses which reach the extensor muscles via the somatic efferent fibers The component of tonus mediated through these fibers is greatly exaggerated Unless the influence of the sympathetic fibers on muscle tonus were equally exaggerated (which is not the case) the absence of the sympathetic influence on the tonus of the muscles of a limb deprived of its sympathetic innervation might easily escape detection, during decerebrate rigidity, except by very accurate quantitative methods In view of the central nervous mechanisms involved and the important role of the somatic efferent fibers in the exaggerated extensor tonus in the extremities of decerebrate preparations, it must be apparent that experiments involving decerebrate rigidity are not well adapted to reveal the influence of the sympathetic nerves on the tonus of skeletal muscles

ried out in mid-brain animals All these animals had been subjected to unilateral extirpation of the stellate ganglion before section of the brain stem was carried out In some instances the measurements were first carried out while the animal was under light ether anesthesia and again several hours after section of the brain stem In most of these experiments, the corresponding tonus curves derived from the measurements obtained before and after section of the brain stem are essentially similar and almost coincident

The tonus curves of both the triceps brachii and the extensor muscles of the manus derived from measurements carried out before sympathetic denervation of the limb (Fig 73, *B* and *C*) like those of the quadriceps femoris, rise very slowly at the beginning and then more rapidly as the length of the muscle is increased by passive extension until flexion of the limb reaches a relatively high degree The tonus curves derived from measurements carried out on these muscles following sympathetic denervation of the limb (Fig 73, *B* and *C*) like the corresponding curves of the quadriceps femoris, rise more rapidly from the beginning These curves indicate that the triceps brachii and extensor muscles of the manus like the quadriceps femoris exhibit diminution of tonus while at rest, following elimination of the sympathetic innervation of the limb

In the results of the experiments set forth above the influence of the sympathetic nerves on the tonus of a resting muscle is manifested only by diminution of the resistance offered by the muscle to passive extension In order to obtain tonus curves which actually represent a component of tonus which is mediated through the sympathetic innervation and at the same time obviate any possible effect of changes in circulation due to interference with the innervation of the blood vessels supplying the limb, tonus measurements were carried out on the triceps brachii muscle following section of both roots of the sixth, seventh and eighth cervical nerves within the spinal canal This operation completely eliminates the somatic innervation of the triceps but, since the preganglionic neurons in the visceral efferent chains supplying the limb are components of thoracic nerves it leaves the sympathetic innervation of the limb intact, consequently, the efferent innervation of blood vessels is not interfered with by the operative procedure Tonus curves based on measurements carried out on the triceps brachii following section of both roots of the sixth, seventh and eighth cervical nerves compared with the normal tonus curves of this muscle (Fig 74) show diminution of tonus but as indicated by the slow rise in the first part of the curve, the muscle still exhibits the brake phenomenon This is well illustrated by curves *R′* and *I′*, Figure 74 *B*, which are the tonus curves of the right and left triceps muscles respectively of the same animal (dog) following section of the roots of the sixth seventh and eighth cervical nerves on the right, and extirpation of the inferior cervical sympathetic ganglion on the left side Since the entire spinal nerve supply to the triceps is derived from the sixth seventh and eighth cervical nerves and the preganglionic fibers involved in the sympathetic innervation of the fore limb emerge mainly below the first thoracic segment section of the roots of the first thoracic nerve has no influence on the tonus measurements carried out on the triceps The curves obtained following section of the roots of the first thoracic, in addition to those of the sixth seventh and eighth cervical nerves, are essentially identical with those obtained follow-

ing section of the roots of only the cervical nerves In order to be of value, these measurements must be carried out within a few days after the operation, since the muscles undergo atrophy following section of their somatic nerve supply and the extensors gradually lose the component of tonus which still was measurable immediately after section of the spinal nerve roots

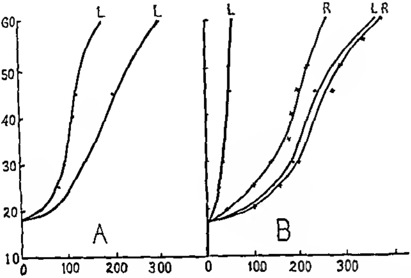


FIG 74 —(A) Tonus curves of the left triceps of a cat before (L) and after (L) section of both roots of the sixth seventh and eighth cervical nerves leaving the sympathetic innervation of the fore limb intact (B) R and L Normal tonus curves of the right and left triceps respectively of a dog R Tonus curve of the right triceps following section of both roots of the sixth seventh and eighth cervical nerves on the right side L' Tonus curve of the left triceps following extirpation of the left inferior cervical sympathetic ganglion

In criticizing the results of our earlier experiments, Fulton (1926) raised the following objections (1) "Experimental analysis of tonic reactions in the intact animals in which various extraneous reflex factors cannot be excluded, are unreliable' (2) "The 'active' muscle not being isolated by complete denervation of the surrounding muscular and cutaneous structures, especially of the antagonistic muscles renders difficult and uncertain the interpretation of their responses (3) Possibly the differences in the resistance of the muscle to passive extension are due to secondary circulatory changes (4) The brake phenomenon "can be little other than a manifestation of the stretch reflex, since it was elicited by extension of an antigravity muscle" He suggested that the diminution in the resistance of the muscle to passive extension indicated by the difference in the curves obtained before and after sympathectomy may be due to modified responses of the proprioceptive endings in the muscle brought about by alterations in the blood supply

The difficulties attending the analysis of tonic reactions in the intact animal are fully recognized We do not regard the results of our experiments as affording the data necessary for an analysis of tonic reactions but only as indicating that the sympathetic nerves exert an influence in the normal tonus of skeletal muscles in the absence of active contraction An influence of the intact flexor muscles is not precluded, but the fact that Spiegel obtained tonus curves of the quadriceps femoris, following section of the tendons of its antagonists, which are essentially identical with the

curves obtained while the flexor tendons were intact, strongly suggests that curves obtained under the conditions of our experiments are not materially modified by the intact antagonists. An influence of circulatory changes due to sympathetic denervation is not precluded in the results of our experiments but there are no data available which clearly indicate that the changes in circulation following sympathectomy exert either a direct or an indirect effect on muscle tonus.

The effect of sympathetic denervation on the so-called brake phenomenon was overemphasized in our earlier reports. We do not regard this phenomenon as dependent on the sympathetic innervation alone although the curves obtained following sympathectomy, in many of our experiments, rise almost as rapidly at the beginning as throughout the latter part of their course. Many of the curves obtained following sympathectomy show clearly that the brake phenomenon still persists. Any appreciable diminution of the resistance of the muscle to passive extension obviously must also affect the brake phenomenon, as manifested in the curves obtained by the method employed in these experiments.

Coates and Tiegs (1925) claim to have repeated our experiments on dogs deprived of the left lumbar sympathetic trunk but were unable to confirm our findings. Their brief report includes no description either of the apparatus used or of the procedure followed. Complete comparability of their experiments to our is not evident since the curve which they derived from measurements carried out on the normally innervated limb does not conform closely to the curves derived from measurements carried out on normally innervated limbs in our experiments. It may be stated in this connection that the curve derived from measurements carried out after sympathectomy was almost identical with the curve obtained before sympathectomy in a few animals in our series but in most of them the difference was unmistakable.

The experimental data set forth above show quite clearly that the resistance of an extensor muscle to passive extension is diminished following sympathetic denervation of the limb and that an extensor muscle deprived of its spinal nerve supply but with the sympathetic innervation of the limb intact still offers greater resistance to passive extension than the completely denervated muscle until the muscle has undergone some degree of atrophy. The loss of the influence of the sympathetic innervation of a limb on the tonus of its muscles, at least in the animals studied by us, is so completely compensated by the cerebrospinal nervous mechanisms under normal physiologic conditions, that the deficiency usually cannot be detected by palpation of the muscles or by direct observation. Delicate quantitative methods are of primary importance in detecting the influence of the sympathetic innervation in the tonus of skeletal muscles. Since the influence of the voluntary innervation is constantly changing during muscular activity, quantitative methods designed to reveal the influence of the sympathetic nerves in skeletal muscle tonus can be successfully applied only while the muscle is at rest, *i. e.* while it does not exhibit active contraction.

The results of our experiments are not expressed in definite units of measurement but they are quantitative. The method used also is sufficiently delicate to reveal changes in tonus which are quantitatively minute. That which actually is measured is the resistance offered by the

muscle to passive extension It may be objected that this is not tonus The tonic state of the muscle however, must be regarded as an important factor in determining the resistance offered to passive extension Since, under the conditions of the experiments the curve of resistance of the atonic muscle is regarded as a vertical line, the curve of resistance of the muscle under complete or partial innervation may properly be regarded as the tonus curve

The tonus exhibited by an extensor muscle, in the absence of active contraction as manifested by the resistance offered by the muscle to passive extension is quantitatively small Any deficiency in tonus due to elimination of the sympathetic nerves, furthermore is quite completely compensated in the normal postures and activities of the animal by the cerebrospinal innervation It is not surprising, therefore that so many investigators have failed, in the absence of quantitative methods to detect any diminution of tonus in the affected muscles following sympathectomy

In view of the data available there is no advantage in postulating a sympathetic component of tonus which differs in quality from the tonus which is mediated through the cerebrospinal nerves The concepts of contractile and plastic tonus may be useful but the theory that plastic tonus is subserved by the sympathetic nerves alone is untenable

The results of tonus measurements carried out on the quadriceps femoris in four patients who underwent bilateral lumbar sympathetic ganglionectomy have been reported (Kuntz 1927) These measurements were carried out according to the method described by Spiegel (1923) for measuring the resistance of the quadriceps femoris in man to passive extension The results obtained by this method are expressed in tonus curves which are comparable to the tonus curves derived from measurements carried out in animals according to Spiegel s method Two of the patients men afflicted with thrombo angiitis obliterans, were available for study both before and after operation The other two were available for study only after operation One of these a young woman had undergone the operation one year previously for the relief of Raynaud s disease the other a man afflicted with thrombo-angiitis obliterans, underwent the operation six days before the measurements were carried out

These patients exhibited no appreciable changes in muscle tonus referable to the disease The tonus curves obtained in the two patients before sympathectomy lie well within the range of normal variation These curves two of which are illustrated in Figure 75, rise slowly until the angle of the leg with the extension of the thigh approaches 30 degrees after which they rise more rapidly They are essentially normal tonus curves The curves obtained after sympathetic ganglionectomy in all the patients, rise more rapidly from the beginning Those obtained from the patients who were available for study before operation also indicate appreciable diminution of tonus In the absence of tonus curves based on measurements carried out before operation in the other two patients the alteration in quadriceps tonus referable to sympathectomy, cannot be estimated but the form of the curves suggests diminution of tonus

Clinical Data —Clinical data bearing on the rôle of the sympathetic nerves in the production and maintenance of muscle tonus are not unequivocal The beneficial effects of sympathetic ganglionectomy and ramisection in the treatment of spastic paralysis, as reported in certain cases,

particularly by Royle (1924 1927) Carroll (1926) Wade (1927), Potter (1927) Stewart (1927) Kure *et al* (1927), Fulton (1928) and von Lackum (1929) strongly suggests that the exaggerated tonus exhibited by the spastic muscles is due at least in part to impulses conducted through the sympathetic nerves Certain other surgeons, notably Kimmel, Pollock and Davis (1925) observed no change in the tonus of spastic muscles following sympathectomy although they applied this operation in a wide variety of cases

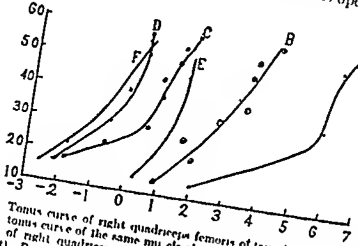


FIG 78 — *A* Tonus curve of right quadriceps femoris obtained just before lumbar sympathectomy *B* tonus curve of the same muscle obtained just after lumbar sympathectomy *C* tonus curve of right quadriceps femoris obtained just before lumbar sympathectomy (another patient) *D* tonus curve of the same muscle obtained just after lumbar sympathectomy *E* tonus curve of left quadriceps femoris (another patient) obtained six days after lumbar sympathectomy *F* tonus curve of left quadriceps femoris (another patient) obtained one year after lumbar sympathectomy

On the basis of a clinical and experimental study of muscle tonus in man by the use of Mosso's apparatus Harer (1925) reported that the resistance of the gastrocnemius and soleus muscles to passive extension is increased by the administration of adrenin pilocarpine or atropine but is diminished by the administration of novocaine or histamine Kure and his associates (1925) reported heightening of the tendon reflex by the administration of adrenin particularly in cases in which these reflexes were already exaggerated before the adrenin was administered They also reported improvement of the muscle tonus, by the use of adrenin in tabetic patients with hypotonic muscles Harer and Kure *et al* interpreted the results as supporting the theory that muscle tonus is maintained in part through the sympathetic nerves The reported results of sympathetic denervation in the treatment of spastic paralysis also afford some data which seem to support the assumption that the sympathetic nerves play a role in the production and regulation of skeletal muscle tonus These data will be reviewed in Chapter XXIV

Sympathetic Nerves and Muscle Fatigue —Certain experimental data seem to indicate quite clearly that the sympathetic nerves play an important role in sustained muscular activity Certain other data, on the contrary fail to support this theory

Hunter (1925) reported that birds with one wing deprived of its sympathetic innervation showed the effect of this deficiency in increasing degree during prolonged flight In contrast to these observations Tower (1926) concluded, on the basis of experiments carried out on dogs, that

"the capacity for prolonged muscular work and the onset and severity of fatigue were in no way affected by sympathectomy"

Coates and Tiegs (1928) reported the results of experiments which seem to indicate a marked effect of the sympathetic nerves on the resistance of an isolated muscle to fatigue In animals (several goats and a dog) which had been subjected to extirpation of the left lumbar sympathetic trunk three to four months earlier, the gastrocnemius or tibialis anterior muscle on both sides was isolated, the branches of the sciatic nerves supplying other muscles were severed and the proximal ends of the sciatic nerves were crushed in order to abolish reflex control of the muscle the tendons of both muscles were attached to levers which recorded on a slowly rotating drum the contractions produced by short tetanic shocks at the rate of 2 to 3 per second Both nerves were stimulated simultaneously from the same induction coil In some instances, the femoral arteries were ligated while the nerves were being stimulated In all but one of their experiments the muscles on the normally innervated side resisted fatigue longer than the one on the sympathetically denervated side

Buttner and Heimbrecht (1928) reported that in frogs which had been subjected to unilateral deprivation of the sympathetic supply to the hind limb, the gastrocnemius muscle on the side of the operation remained shortened, after strong contractions 95 per cent longer than the one on the unoperated side They also reported that when both gastrocnemius muscles were thrown into complete tetanus the curve of contraction of the muscle in the limb deprived of its sympathetic innervation dropped more rapidly than that of the one in the normally innervated limb in three-fourths of the cases Schneider (1929 1930) failed to corroborate these findings Ginetzinsky (1922) reported experiments in which the isolated gastrocnemius of the frog was stimulated through its motor nerves by short tetani five seconds in duration at intervals of fifty-five seconds and isometric records obtained The plateau tension developed in each successive response diminished progressively under these circumstances but when the sympathetic trunk was stimulated during the fifty-five second intervals, the diminution in the plateau tension did not occur during the first five or six tetanic responses In another series of experiments Ginetzinsky (1926) brought about fatigue of the gastrocnemius of the frog in an atmosphere of hydrogen by stimulation of the motor nerves In most of these experiments (75 per cent) stimulation of the sympathetic trunk following the onset of fatigue also resulted in increasing the strength of the contractions and the resistance of the muscle to fatigue This result was interpreted as showing that the effect of sympathetic stimulation on muscular activity is not due solely to increased oxidation of the products of metabolism It strongly suggests that sympathetic stimulation actually retards the onset of fatigue

In experiments carried out by Orbeli (1924 1925) the isolated gastrocnemius of the frog was made to contract at repeated short intervals (30 to 300 per minute) by stimulation of the ventral roots of the seventh, eighth and ninth nerves When the onset of fatigue became apparent in the diminution of the amplitude of the successive contractions the sympathetic trunk was stimulated for twenty to sixty seconds and after a latent period of ten to thirty seconds the amplitude of the successive contractions again increased, the maximum effect occurring some time after the sympathetic

stimulation had ceased. This reaction, known as the Orbeli phenomenon also suggests that sympathetic stimulation tends to increase the resistance of skeletal muscles to fatigue.

In contrast to the results reported by Ginetzinsky and Orbeli, Wastl (1925) failed to demonstrate a direct effect of sympathetic stimulation on the activity of a muscle following the onset of fatigue either in the frog or the cat. Jaschwili (1928) also failed to corroborate Orbeli's findings. He reported that sympathetic stimulation resulted in augmentation of the contractions of the muscles even in the absence of fatigue when the stimulation was submaximal but not when it was supermaximal.

Maibach (1928) reported the results of experiments which may be regarded as a repetition of experiments reported by Orbeli. They were carried out with more refined technic and under more rigidly controlled conditions. Using bloodless preparations of the frog, the isolated gastrocnemius or gracilis muscle was made to contract at uniform short intervals by stimulation of the ventral roots of the eighth and ninth spinal nerves. The sympathetic trunk was stimulated by means of a current just above the threshold of sympathetic stimulation at various intervals during the activity of the muscle. Like Orbeli, Maibach found that when the sympathetic trunk was stimulated following the onset of fatigue of the muscle as indicated by the gradual diminution of the amplitude of the contractions, the amplitude gradually increased after a latent period of several seconds, reached a maximum and then gradually decreased. The effect of sympathetic stimulation always continued for a short time after stimulation of the sympathetic trunk ceased. The results obtained with the muscle in air but kept moist by frequent applications of a physiologic salt solution and with the muscle immersed in a bath designed to compensate as nearly as possible for the lack of circulation and respiration were comparable although the muscle became fatigued more rapidly under the former than under the latter conditions. Stimulation of the sympathetic trunk before the onset of fatigue of the muscle had no effect on the amplitude of the contractions. Maibach therefore concluded that muscular contraction is augmented by sympathetic stimulation only after the muscle has become somewhat fatigued.

The results reported by Maibach fully corroborate those of Orbeli. Like the latter he concluded that sympathetic stimulation during muscular activity increases the capacity of the muscle to resist fatigue. Since the preparations used were bloodless and comparable results were obtained both with the muscle in air and in a bath designed to restore physiologic conditions as nearly as possible, the increased capacity of the muscle to resist fatigue cannot be regarded as the result of changes brought about through the vasomotor mechanism in response to sympathetic stimulation but must be regarded as the effect of impulses conducted through sympathetic fibers. In view of the experimental technic employed and the results reported by Maibach it seems highly probable that the reported failures to corroborate Orbeli's findings were due mainly to faulty technic.

Labhart (1929) confirmed the findings of Maibach and advanced additional experimental evidence of the augmenting effect of sympathetic stimulation on the activity of fatigued muscle in the frog. When the muscle became fatigued by stimulation of the ventral nerve roots in his experiments, single induction shocks applied to the sympathetic trunk at

one second intervals increased the amplitude of the contractions The restoration of the muscle brought about in this manner lasts longer, according to Labhart than that which is brought about by tetanic stimulation of the sympathetic trunk He also reported that if the fatigued muscle is allowed to recover by decreasing the frequency of stimulation of the ventral nerve roots and at the same time single induction shocks are applied to the sympathetic trunk the effects are summated Nakamschi (1927, 1928, 1930) and Geršuni and Chudoroševa (1930) also reported the results of

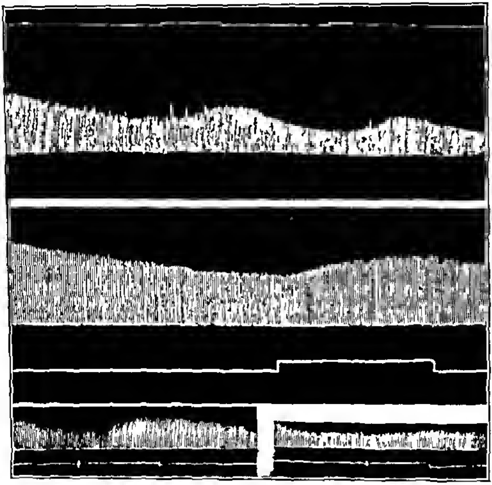


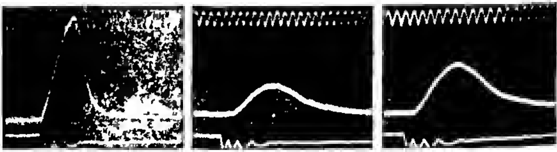
Fig 76 —The effect of sympathetic stimulation on an active skeletal muscle of the frog Successive contractions of the gastrocnemius or gracilis muscle were elicited by stimulation of the ventral roots of eighth and ninth spinal nerves After the onset of fatigue the sympathetic trunk was stimulated at intervals indicated by the time signal It will be seen that the amplitude of the contractions gradually increased after a latent period (*A* from Orbeli Pavlov Jubilee volume 1924 *B* and *C* from Maibach Ztschr f Biol 1928 vol 88 No 3 München Germany J T Lehmann s Press)

experiments in which the effects of sympathetic stimulation on the fatigued gastrocnemius muscle of the frog were observed which in general corroborate Orbeli s findings Sinizin (1937) studied the effect of sympathetic stimulation on the curve of fatigue of the frog s gastrocnemius under the following conditions direct stimulation successive direct and indirect stimulation during infusion with a solution of curare and following degeneration of the somatic nerves Under all these conditions, according to his account sympathetic stimulation resulted in delaying the onset of fatigue

Van Dijk (1930) reported that when the triceps muscle of the decere-

brated pigeon was fatigued by stimulation of the motor nerves for several hours stimulation of the sympathetic trunk usually increased the amplitude of the contractions but sometimes decreased it Baetjer (1930) likewise reported that when the tibialis anticus of the cat, in his experiments, was undergoing rhythmic contractions elicited by single induction shocks applied to the ventral nerve roots, superadded stimulation of the sympathetic trunk sometimes resulted in increasing and sometimes in decreasing the amplitude of the contractions He regarded augmentation of the contractions, under these conditions as the direct result of impulses which reach the muscle through the sympathetic nerve fibers and diminution of the contractions as an indirect result of vasoconstriction Chudoroševa (1932) reported an augmenting effect of sympathetic stimulation on the contractions of fatigued muscles and pointed out that this effect is more marked three or four days after section of the motor fibers than while the motor fibers are intact These results also may be regarded as in agreement with Orbeli s findings

Charlet (1930) employed a method by which the effect of sympathetic stimulation on the isometric contractions of fatigued muscle in the frog was recorded photographically According to his records sympathetic stimulation results in a steeper rise in the curve of isometric contraction of the fatigued muscle The height of the curve also is increased but the duration of the entire contraction is unaltered (Fig 77)



a b c

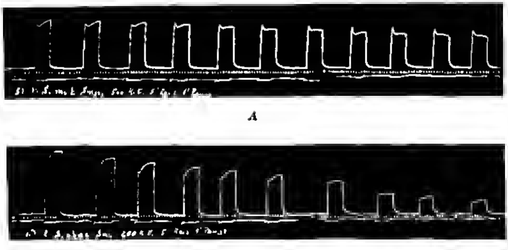
Fig 77 —Isometric contraction curves of the frog s muscle a Normal muscle b fatigued muscle c same as b but with sympathetic stimulation (Charlet Ztschr f Biol 1930 vol 90 No 4 München Germany J T Lehmann s Press)

Michol (1930) reported the results of a series of experiments in which the effect of sympathetic stimulation of muscles of the frog fatigued by direct stimulation was recorded In these experiments the nerve to the muscle was curarized so that electric stimulation of the nerve trunk did not produce contraction The muscle was then fatigued by direct rhythmic stimulation When fatigue had set in stimulation of the nerve trunk resulted in increasing the amplitude of the contractions called forth by direct stimulation This result was interpreted as indicating restitution of the muscle brought about by stimulation of the sympathetic fibers in the nerve trunk When the motor end-plates were rendered ineffective due to the lack of calcium, in Michol s experiments, sympathetic stimulation was without effect on the contractions called forth by direct stimulation

Schnyder (1936) reported the results of experiments carried out on rabbits which are comparable to those reported by Michol When in his

experiments, the mixed nerve supplying a muscle was stimulated by means of a stimulus above the threshold for the sympathetic fibers, the onset of fatigue occurred appreciably later than when the motor fibers alone were stimulated

Voser (1931) reported the results of experiments in which the effects of sympathetic stimulation on the normal reflex responses of fatigued muscles in the frog were studied In his animals, either the cerebrum alone or the entire brain was destroyed, but the circulation was left intact The sympathetic rami joining the nerves to one hind limb were divided and the skin or an appropriate afferent nerve on that side was stimulated to elicit reflex contraction of limb muscles on both sides Records of the simultaneous reflex contractions of the muscles of both hind limbs elicited by repeated stimulation of the skin or an afferent nerve on the sympathectomized side at short intervals show that the amplitude of the successive contractions decreases more rapidly on the sympathectomized than on the normal side (Fig 78, *A* and *B*) On the basis of these experiments, the



A

B

FIG 78 —Records of simultaneous contractions of corresponding muscles of the frog s hind limb with the sympathetic supply intact on one side (*A*) and removed on the other (*B*) (Voser Ztschr f Biol 1931 vol 91 No 2 Munchen Germany J T Lehmann s Press)

author concluded that the muscles normally receive impulses through their sympathetic innervation and that deprivation of these impulses reduces their capacity for work He also regarded his findings as corroborating those of Maibach Labhart Charlet and Michol and advanced the opinion that the results obtained can be explained only on the assumption that sympathetic fibers actually terminate in relation to the skeletal muscles since under the conditions of his experiments, the changes in the blood supply to the limb muscles resulting from the operative procedure favors the muscles on the sympathetomized side

Haller (1932), by means of an oscillograph of high frequency, recorded the action currents produced by reflex contractions, elicited by equal stimuli of corresponding muscles of both hind limbs of decerebrated frogs with the abdominal portion of the sympathetic trunk on one side removed The action currents produced on the sympathectomized side always were weaker, of shorter duration and of lower frequency than those produced on the normally innervated side Notter (1936) recorded action currents by

means of the cathode ray oscillograph in the gastrocnemius muscle of the frog due to reflex stimulation following section of the corresponding motor nerve roots. Such action currents could not be recorded following section of both the motor nerve roots and the sympathetic rami. Both Haller and Notter concluded, on the basis of their experimental findings, that nerve impulses conducted through the sympathetic fibers normally exert an influence on the activity of skeletal muscles.

According to Lapicque and Lapicque (1930) and Lapicque (1931) fatigue in skeletal muscles is accompanied by an increase in the chronaxie of the muscles while the chronaxie of the nerves remains unchanged, consequently the synchronism between the chronaxies of the muscles and nerves is disturbed. They advanced certain experimental data which seem to indicate that sympathetic stimulation following the onset of muscle fatigue decreases the chronaxie of the muscle, tending to restore the synchronism between the chronaxie of the nerves and that of the muscles. This they regard as the explanation of the restitution of fatigued muscle brought about by sympathetic stimulation. Volochov and Gersuni (1933) also reported shortening of the chronaxie in fatigued nerve-muscle preparations of the frog due to sympathetic stimulation.

The results obtained by all the investigators cited above who observed restitution of fatigued muscle brought about by sympathetic stimulation seem to be in accord with most of the data available regarding the effect of adrenin on fatigued muscle. Cannon and Nice (1913) observed an increase in the working power of the tibialis anticus in the cat following stimulation of the peripheral end of the splanchnic nerve. This result was regarded as due at least in part to the action of adrenin on the muscle. In Gruber's (1924) experiments, injection of adrenin increased the amplitude of contraction, lowered the threshold of stimulation and shortened the latent period of both fatigued and unfatigued muscle. He therefore suggested that adrenin may exert a direct "trophic" action on the muscle presumably through facilitation of the removal of metabolites. In Maibach's (1928) experiments the addition of adrenin in appropriate amounts to the bath in which the muscle was immersed following the onset of fatigue produced an effect similar to that of sympathetic stimulation. Hodes (1939) also reported improvement of fatigued muscles in sympathectomized cats following the injection of adrenin. Although certain investigators have failed to observe a direct effect of sympathetic stimulation on the capacity of skeletal muscles to resist fatigue, we do not regard such negative findings as constituting an adequate reason to question the corroborative evidence afforded by the positive findings reviewed above. The latter have an important bearing on the functional relationship of the sympathetic nerves to skeletal muscles, since any mechanism through which the capacity of skeletal muscles to resist fatigue is augmented must be of fundamental importance to the organism.

Site of Action of Sympathetic Nerves on Skeletal Muscles.—The results of much of the earlier experimental work bearing on the influence of sympathetic nerve impulses on skeletal muscles seemed to support the assumption that such impulses are transmitted directly to the muscle fibers. Many data available at present do not support this assumption. Orbeli advanced the hypothesis, on the basis of his findings, that the sympathetic nerves exert their influence on skeletal muscles through the peripheral apparatus

of the motor nerves. Certain observations of Weiss (1930) also seem to support this hypothesis.

In a series of experiments, the results of which have not been published elsewhere, Kuntz and Kerper obtained certain evidence which seems to support the theory that the sympathetic nerves exert an influence on the irritability of the muscle fibers in some manner. These experiments were designed to show the effect of sympathetic denervation of a limb on the facility with which viscerosomatic reflexes are elicited by stimulation of the visceral organs or mesenteric nerves. The experimental animals (cats) were subjected to unilateral extirpation of the lumbar and upper sacral portions of the sympathetic trunk. The spinal cord was transected at the level of the foramen magnum. After the initial shock of the latter operation had subsided, the visceral organs or mesenteric nerves were stimulated either mechanically or by means of an electric current. In all the animals in which the experiment was successful, reflex responses to both mechanical stimulation of visceral organs (pressure on the spleen, duodenum or pancreas, inflation of the stomach, etc.) and electrical stimulation of mesenteric nerves were observed in the hind limb on the side on which the sympathetic trunk was left intact, but rarely in the hind limb deprived of its sympathetic innervation. Viscero-somatic reflexes involving the muscles of the hind limb on the sympathectomized side could only be elicited by much stronger visceral stimulation than that required to elicit fairly vigorous reflex responses in the normally innervated limb. In some animals no reflex muscular reactions in response to visceral stimulation were observed in the hind limb deprived of its sympathetic innervation, although the stimulation employed was sufficiently strong to elicit vigorous reflex responses in the normally innervated hind limb. Under the conditions of these experiments the viscero motor reflex arcs on the side of the sympathectomy were not impaired. It seems not improbable, therefore, that the difference in the degree of reactivity of the muscles of the two hind limbs to visceral stimulation was due to the presence in the one limb of the intact sympathetic nerves and their absence in the other.

The results of the experiments of Maibach, Labhart, Charlet, Michol, Voser, Haller and Notter cited above, all of which were carried out in Asher's laboratory, seem to support the hypothesis that the effect of impulses reaching the skeletal muscles through sympathetic nerve fibers is exerted on some mechanism within the muscle fibers and not on the motor end plates. On the basis of these experiments, in which the effects of sympathetic stimulation on the skeletal muscles were observed only after the onset of fatigue, Asher (1931) advanced the theory that the substratum on which the sympathetic nerves act is lacking in the unfatigued muscles, but arises with the onset of fatigue. He (1932) also reported the results of other experiments carried out in his laboratory which indicate that sympathetic stimulation results in an increase in the phosphoric acid content of the muscle, which probably plays an important role in its restitution following the onset of fatigue.

In view of all the data which support the theory that sympathetic nerve impulses are mediated through humoral substances, the assumption that sympathetic stimulation influences skeletal muscles only after the onset of fatigue seems to be unwarranted. On the contrary, the humoral mediators

liberated as a result of sympathetic nerve stimulation undoubtedly influence unfatigued as well as fatigued muscle.

The experimental data cited in the preceding pages are not incompatible with the hypothesis that the influence of the sympathetic nerves on skeletal muscles is mediated through humoral substances. This hypothesis is further supported by the results of experimental studies bearing directly on the problem of humoral mediators. Corkill and Tiegs (1935) advanced experimental evidence in support of the assumption that the increase in the strength of contraction of a fatiguing muscle brought about by sympathetic stimulation (Orbeli phenomenon) is effected through a humoral agent. They also pointed out that this phenomenon can be reproduced by appropriate treatment with adrenin. Tiegs (1934) reported further that stimulation of the sympathetic nerves to the skinned hind limbs of the frog results in the liberation of a substance which has the capacity to increase the strength of contraction of an isolated heart or another muscle into which it is perfused. Data reported by Schmid (1936), Brack (1936) and Meis (1937) also support the assumption that the increased heat production in skeletal muscle which results from sympathetic stimulation is effected through humoral agents.

The exact sites of the liberation of the hormonal substances in question as yet are unknown. Those who do not admit the existence of sympathetic nerve-fiber terminations on skeletal muscle fibers cannot assume that these substances are liberated in immediate contact with the muscle fibers or within them. In view of the properties of the humoral mediators it is not inconceivable that all the observed effects of sympathetic stimulation on skeletal muscles could be brought about through such mediators liberated in the walls of the blood vessels or in immediate proximity to them.

Sympathetic Nerves and Muscle Metabolism.—Certain investigators have maintained that the ratio of the creatinin to the creatin content of skeletal muscle is determined at least in part by influences exerted through the sympathetic nerves. Creatin metabolism, however, is increased during muscular activity; consequently, it cannot be dependent on sympathetic influences alone. As has been pointed out by Langley (1922), the data bearing on this point indicate that creatin metabolism is influenced to a far greater extent by the somatic than by the sympathetic nerves.

According to Büttner (1926, 1929), the glycogen content of muscles is increased following sympathetic denervation. The results of certain of his experiments also indicate an increase in the lactic acid content of the muscles. Hoffmann and Wertheimer (1927, 1928) observed no appreciable changes in the glycogen content of the gastrocnemius and vastus muscles of the frog within a few days after sympathetic denervation. When animals (cats and dogs) were starved, following unilateral section of the sciatic nerve in their experiments, the glycogen content diminished much less rapidly than that of the normally innervated muscles. In animals which had been starved before section of the sciatic nerve and then fed abundantly the glycogen content of the denervated muscles was not appreciably increased. In animals which had been subjected to unilateral sympathectomy more glycogen was found on the operated side than on the other following the administration of strychnine or adrenin. Britton (1930) reported marked diminution in the glycogen content of the limb muscles of the cat during many weeks following sympathetic denervation.

This result, he believes, is not referable to circulatory changes Herrin and Meek (1931) reported reductions of 12 to 20 per cent in the glycogen content of the tonic muscles in dogs and rabbits twenty to eighty-six days after sympathectomy In animals with hyperthyroidism, the reductions in the glycogen content of the muscles following sympathetic denervation were even greater Wenger (1933), who measured the heat generated in the same muscles on both sides following reduction of body temperature by cooling and in the presence of chemically induced fever, in animals which had been subjected to unilateral sympathectomy, always found the generation of heat greatest on the normally innervated side In experiments reported by Schmid (1936) the muscles of the forelimb and the masseter muscle on the normally innervated side in rabbits which had been subjected to unilateral cervical sympathectomy, became warmer while working than those on the sympathectomized side, whereas the latter were warmer than the former while at rest Barron (1934) and Scheinfinkel (1938) also reported that cooling of the body of an unilaterally sympathectomized animal resulted in greater heat production as determined by thermoelectrical measurements in the muscles on the normally innervated side than in the affected muscles on the sympathectomized side These findings strongly suggest that glycogen metabolism in skeletal muscles is subject to regulation through the sympathetic nerves

The influence of the sympathetic nerves on the processes of oxidation and reduction in skeletal muscles is well illustrated by the effect of sympathectomy and sympathetic stimulation on the reaction of the muscles to vital dyes When a vital dye, *e g* methylene blue is injected into the lymph hearts of a frog the muscles of the extremities become lightly stained Hoffmann and Magnus-Alsleben (1922) observed that if the nerves supplying one of the hind limbs are cut following the injection of methylene blue into the posterior lymph hearts, the muscles of that limb assume a more intense color than those of the other hind limb In a further investigation of this phenomenon they found that neither section of the dorsal nerve roots nor paralysis of the motor components alone exert an influence on the staining reaction of the muscles When the communicating rami of the seventh eighth and ninth nerves were divided leaving the dorsal and ventral nerve roots intact the muscles of the hind limb on this side assumed a more intense color than when the entire nerve supply to the limb was cut This seemed to prove that the observed difference in the staining reaction of the muscles of the two hind limbs was due to section of the sympathetic fibers They also demonstrated that the more intense staining reaction of the muscles deprived of their sympathetic innervation was not due to an excessive amount of the dye taken up by the muscle fibers but to retardation of the processes of reduction When the lightly stained muscles of the normally innervated limb were treated with oxidizing agents, they also became intensely blue

On the basis of results obtained in experiments designed to demonstrate the effect of sympathetic stimulation on the reaction of the skeletal muscles to methylene blue Stepanoff (1923) and Krestownikoff (1926), working in Orbeli s laboratory reported that the oxidative processes in skeletal muscle are augmented by sympathetic stimulation By the use of the mikrorespirometer Orbeli also demonstrated a relative increase in O_2 consumption in skeletal muscles during sympathetic stimulation This

relative increase in the oxidative processes was manifested *mainly in the* retardation of the continuous decrease in O_2 consumption during muscular excitation and in the fact that the oxygen intake remained constant during sympathetic stimulation and for some time after its cessation.

Sympathetic denervation is followed by dilatation of the capillaries in skeletal muscles. The duration of such capillary dilatation is not definitely known. Some data bearing on this point have been interpreted as indicating that, in experimental animals (cat, dog, rabbit), the circulation through a limb deprived of its sympathetic innervation approximates the preoperative level within ten days or two weeks after operation. Britton (1930), however, has demonstrated by actual measurements of the volumes of blood per minute flowing through the respective hind limbs of cats *following unilateral lumbar sympathectomy, that a marked increase in the* volume of blood flowing through the capillary bed of the sympathectomized limb is maintained at least for many weeks. Sympathetic denervation also results in increased permeability of the capillaries which plays an important role in the metabolic changes observed in skeletal muscles after sympathetic denervation. It need not be assumed, however, that all the metabolic changes referable to sympathetic denervation are due to vascular changes. On the basis of the results of experiments involving ligation of the blood vessels and the injection of caffein in doses sufficient to produce maximal vasoconstriction and irreversible rigidity, Büttner (1926) concluded that the metabolic changes observed in skeletal muscles following sympathectomy are brought about, at least in part, by the direct effects of *elimination of the influence of sympathetic nerve impulses on the muscles.* In this connection it is not without interest to recall that Claude Bernard (1871) discussed the possibility of a sympathetic influence in muscle metabolism which is independent of vasomotor control.

CHAPTER XVIII

HISTOPATHOLOGY

INTEREST in the autonomic nervous system in relation to disease has increased with increasing knowledge of the physiologic relationships of the autonomic nerves but the advances in our knowledge of the histopathologic changes in the autonomic ganglia and nerves and the central autonomic centers have not kept pace with the advances in the various aspects of the physiology of the autonomic nerves Most of the studies bearing on the role of the autonomic nervous system in disease deal mainly with the clinical and pharmacologic aspects of the problem Varied and extensive pathologic changes in the autonomic ganglia and ganglion cells have been described but the data bearing on the specific relationships of these changes to particular diseases are relatively meager

Histopathologic studies have been carried out mainly on preparations of material obtained at autopsy following deaths due to a wide variety of causes and preparations of ganglia removed by operation in the treatment of a limited group of diseases In most instances it was quite impossible to establish a direct relationship between the neural lesion in question and a given disease process, due to the variety of pathologic conditions present which not infrequently included some degree of senile degeneration In spite of these difficulties the available data strongly suggest a direct relationship of recognizable lesions of the autonomic nervous system and the disease process in many acute and chronic clinical conditions More exact knowledge of the nature and the causes of lesions of the autonomic nervous system and their relation to disease must await further clinical and experimental investigation

Ganglia and Ganglion Cells —Chromidial Substance and Nucleus plasma Ratio —Most investigators who have reported the results of histopathologic studies of autonomic ganglion cells have described alterations in the chromidial substance involving changes in its abundance and distribution in the cytoplasm and alterations in the chromatin in the nucleus In many instances attempts have been made to correlate the observed changes in the ganglion cells with a particular disease process but in relatively few instances have attempts been made to interpret the changes in the ganglion cells in terms of modified function

Functional activity and depression of nerve cells result in changes in the quantity and distribution of their chromidial content In an extensive series of studies of the cytologic changes brought about in nerve cells by physiologic stimulation and depression under experimental conditions Dolley (1909–1918) found that changes in the quantity and distribution of the chromidial substance and variation in the nucleus-plasma ratio are natural consequences of functional activity and depression of these cells and conform to the well-recognized biological principles expressed in Goldschmidt s (1904) theory of the functional significance of the chromidial apparatus and Hertwig s (1903) theory of the nucleus plasma ratio The latter theory expresses a constant mass relationship but carries with it an underlying reciprocal principle, the mutual interdependence and inter-

change of materials. In the nerve cells, as in many other cells, this interchange of materials involves the production and consumption of chromidial substance. Both nucleus and cytoplasm take part in the elaboration of this substance, and it is concerned mainly with function in the cell. During cellular activity, chromidial substance disappears not only from the cytoplasm but also from the nucleus. The cell may become practically dechromatinized but after due rest, it regains its full complement of chromidial substance.

The orderly sequence of change involving the chromidial substance and the nucleus plasma ratio in the Purkinje cells in experimental animals subjected to continued stimulation was described by Dolley (1911) as follows. The cell, which in the resting condition contains a variable amount of extranuclear chromidial substance and little intranuclear chromatin except in the nucleolus, first responds by increased chromatin production and becomes progressively hyperchromatic until the initial enlargement of the whole cell reaches its maximum. Following the stage of hyperchromatism, the cell begins to shrink and the hyperchromatism recedes until the chromidial content of the cytoplasm has become reduced to the average normal level but the nucleus shows evidence of edema, consequently, the nucleus plasma ratio is shifted in favor of the nucleus. The chromidial content of the cytoplasm suffers still further diminution until the secondary restoration of the cytoplasmic chromidial substance sets in. The newly formed chromidial substance is first piled up about the nuclear membrane and then displaced toward the periphery. Following this stage secondary diminution of the chromidial substance sets in and continues until no chromatic material remains apparent except in the nucleolus. Finally the also passes out and the cell appears pale and exhausted. During the final stages of exhaustive activity the nucleus-plasma ratio is shifted in favor of the plasma. In view of this succession of changes in the cell, it may be assumed that the chromidial substance in the cytoplasm, derived through the nucleus, is used up during cellular activity and continually replaced by the mediation of the nucleus. At first the supply exceeds the demand giving rise to hyperchromatism, but with long-continued activity the supply no longer equals the demand and the chromidial substance undergoes a progressive diminution until finally none remains in the cell.

Functional depression of a nerve cell may intervene during any phase of functional activity. The immediate result of functional depression, according to Dolley (1913), is cessation of extranuclear chromatic production. The extranuclear chromidial substance is gradually consumed but the intranuclear chromatin cannot pass out, consequently there is a relative or absolute increase of intranuclear chromatin associated with a deficiency of cytoplasmic chromidial substance and the nucleus plasma ratio is shifted in favor of the nucleus. If long-continued, depression becomes a degenerative condition, shrinkage and dissolution of the nucleus take place and the cell may become reduced to a shrunken, anucleated homogeneous hyaline mass.

The results of Dolley's anatomic analysis of the effects of stimulation and depression on nerve cells are in full accord with the recognized physiologic classification of stimuli into three groups (1) pure excitants (2) pure depressants and (3) those which first excite and later depress. While there is a separate anatomic basis for fatigue of excitation and fatigue of

depression, the manifestations of these two forms of fatigue must be identical In exhaustive activity, the production of chromidial substance fails, in depression, it is inhibited Although nerve cells do not possess the capacity for rejuvenescence, they have the capacity for recovery within relatively wide limits The process of recovery, whether from the effects of stimulation depression or disuse atrophy involves the restoration of the same preexisting materials and, unless pigmentation has intervened, the cell may resume its normal cytologic appearance

Dolley's studies cited above involve mainly the Purkinje cells in the cerebellar cortex Comparable studies of the effects of stimulation and depression on autonomic ganglion cells are not available Bradshaw (1930) on the basis of a study of the effects of roentgen-ray radiation, and Ingersoll (1934) on the basis of a study of the effects of stimulation of the abdominal viscera on the celiac ganglion cells in the albino rat reported a sequence of changes in the chromidial substance and the nucleus-plasma ratio which in the main, parallels that described by Dolley in the Purkinje cells On the basis of a detailed study of preparations of the celiac ganglia of normal resting rats they classified the ganglion cells into 9 types according to the quantity and distribution of the chromidial substance in the cytoplasm and the nucleus-plasma ratio The cells of the first 3 types which may be regarded as Group I, make up the great majority of the ganglion cells present They possess abundant chromidial substance which is distributed more or less uniformly throughout the cytoplasm Those of the second 3 types which may be regarded as Group II, usually are present in relatively small numbers On the average, they are somewhat smaller than the cells of Group I and possess less chromidial substance which usually is distributed mainly in the perinuclear or the peripheral zone Those of the last 3 types, which may be regarded as Group III, also are present in small numbers On the average these cells are somewhat smaller than those of Group II and possess still less chromidial substance some of them being almost devoid of this material and having but little chromatin in the nucleus By differential counting of the cells in the several groups in preparations of the celiac ganglia from normal resting animals and from animals which had been subjected to manipulation of the abdominal viscera, under anesthesia for periods of varying duration, Ingersoll demonstrated a progressive decrease in the percentage of the ganglion cells in Group I and an increase in the percentage of those in Group III as the length of the period of stimulation was increased The numbers of cells in Group II changed relatively little with stimulation Prolonged administration of nicotine resulted in comparable changes in the celiac ganglion cells in rabbits (Ingersoll, 1936)

According to Ingersoll's findings, the initial response of the celiac ganglion cells to stimulation like that of the Purkinje cells in Dolley's experiments, appears to be increased production of chromidial substance, resulting in hyperchromatism slight enlargement of the cells and a slight shift in the nucleus plasma ratio Following this stage, the chromidial substance is reduced until it approaches the normal level and the cell undergoes some reduction in size with a shifting of the nucleus-plasma ratio in favor of the nucleus Secondary restoration of the chromidial substance is less apparent than in the Purkinje cells but probably is evidenced by the perinuclear distribution of this substance in many of the

cells in Group II Following this stage, the chromidial substance becomes further reduced if stimulation is continued, until the cytoplasm is practically devoid of this substance The nucleus having given up most of its chromatin, also appears pale and vesicular and usually is located eccentrically Following the initiation of stimulation the production of chro-

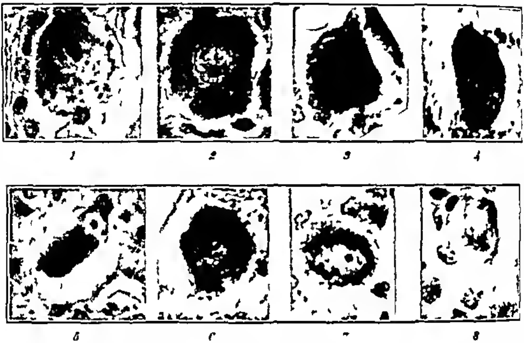


FIG 79 — Autonomic ganglion cells (human) illustrating the progressive changes in the quantity and distribution of the chromidial substance and the nucleus-plasma ratio due to cellular activity *1* Resting cell *2* early hyperchromatism *3* advanced hyperchromatism *4* early shrinkage of the cell and receding hyperchromatism *5* advanced shrinkage of the cell and further recession of hyperchromatism *6* reduction of cytoplasmic chromidial substance to normal level with edema of both nucleus and cytoplasm resulting in rounding out of the cell *7* further reduction of the cytoplasmic chromidial substance *8* almost complete depletion of the cytoplasmic chromidial substance and extrusion of the nuclear chromatin into the cytoplasm

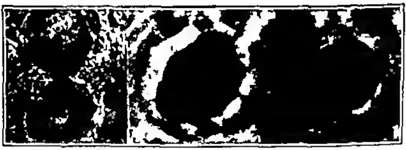


FIG 80 —Autonomic ganglion cells (human) illustrating successive stages in functional depression

midial substance exceeds its consumption giving rise to hyperchromatism Later, the requirements of the cell exceed its capacity to produce chromidial substance and its supply gradually becomes depleted

In preparations of human sympathetic ganglia removed by operation in a variety of diseases including chronic polyarthritis Raynaud s disease and progressive muscular dystrophy, and sympathetic ganglia removed at

autopsy in a variety of pathologic conditions Kuntz (1934) recognized variations in the quantity and distribution of the chromidial substance which conform very closely to the cell types described by Bradshaw and Ingersoll in the celiac ganglia in the albino rat and the series of changes described by Dolley in the Purkinje cells, particularly in the dog, during excitation and depression Some of these variations are illustrated in Figures 79 and 80

In preparations of ganglia removed surgically in cases of essential hypertension and thrombo-angiitis obliterans most of the ganglion cells exhibit marked reduction in the quantity of the chromidial substance in the cytoplasm and some reduction in the chromatin in the nucleus (Fig 81) In these conditions the reduction in the chromidial substance appears to be due to limitation of the blood supply to the ganglion and the consequent reduction of the nutrition of the ganglion cells The chromidial substance which remains is finely granular and quite uniformly distributed in the cytoplasm and the ganglion cells exhibit no apparent restorative reaction

FIG 81 —Photomicrograph from a section of a celiac ganglion removed surgically from a patient with hypertension The ganglion cells appear almost devoid of chromidial substance probably due *to limitation of the blood supply* caused by partial occlusion of arteriole

Certain pathologic conditions result in more profound changes in the chromidial content of the autonomic ganglion cells than others probably due to their stronger stimulating or depressing effect For example in arsenic poisoning and poliomyelitis the chromidial bodies in the autonomic ganglion cells break up and the chromidial substance apparently goes into solution In many cases the chromatolysis involves the majority of the autonomic ganglion cells and in some instances terminates in complete disintegration of many of these cells The changes observed in the autonomic ganglion cells in cases of arsenic poisoning correspond to the changes which have been described in the neurons in the central nervous system in similar cases In addition to chromatolysis they involve homogeneous swelling of the protoplasm and displacement of the nucleus

toward the periphery The occurrence of chromatolysis in the autonomic ganglion cells in cases of poliomyelitis shows clearly that this disease involves the autonomic ganglia as well as the gray substance in the spinal cord

During senility and cachectic states, the study of the changes in the chromidial substance is rendered more difficult by the presence of pigment in the ganglion cells In general it may be stated that heavily pigmented ganglion cells contain relatively small amounts of chromidial substance Careful study of the ganglion cells which are only moderately pigmented in cases of senility or other conditions in which most of them are laden with pigment not infrequently reveals evidence of chromatolysis The larger chromidial bodies in the peripheral zone of the cytoplasm become fragmented while the chromidial substance in the perinuclear zone appears in the form of minute particles (chromidial dust) or is actually in solution leaving *a perinuclear zone which apparently is free from chromidial substance* Fragmentation of the chromidial bodies and chromatolysis may continue until all the chromidial substance in the cell seems to be in solution In Nissl preparations such ganglion cells exhibit a homogeneous blue color with possibly a few heterogeneous patches (Nissl 1892, Laignel Lavastine 1906 Spiegel and Adolf 1922) In cases of death due to burns many of the autonomic ganglion cells exhibit fragmentation of the chromidial bodies clumping of the chromidial substance particularly in the peripheral zone and chromatolysis (Spiegel and Adolf, 1922)

Rapid disintegration of the chromidial bodies in the autonomic ganglio cells also has been observed in many cases of acute infection Som degree of chromatolysis in many cases almost complete dissolution of th chromidial substance has been reported by Mogilnizky (1923) in cases pneumonia septicemia, diphtheria tetanus and miliary tuberculosis

Pigmentation —The occurrence of pigment in autonomic ganglion cel is of peculiar interest in relation to intracellular metabolism Althoug pigment is observed only rarely in the autonomic ganglion cells in anima (cat dog rabbit) except under experimental conditions a moderat degree of pigmentation of these cells is a common phenomenon in ma after middle age, and not infrequently occurs even in the young Whi moderate pigmentation of the autonomic ganglion cells does not necessaril indicate morbidity exaggerated pigmentation of these cells probabl always is pathologic *Certain pathologic conditions e g* arsenic poisoning cachexia and senile atrophy, always are accompanied by exaggerate pigmentation and other evidences of degenerative changes in the autonomic ganglion cells

The pigment observed in the autonomic ganglion cells in man is mainl of two kinds (*a*) yellow lipoid pigment which is at least partially solubl in alcohol ether and other fat solvents and reacts to fat stains and (*b* darker more stable pigment which is highly insoluble In addition t these pigments Marinesco (1906) described certain eosinophile granule which he regarded as related to the yellow pigment and certain cyanophil granules which he regarded as related to the melanotic pigment in th spinal ganglion cells Spiegel and Adolf (1922) observed neither eosinophile nor cyanophile granules in autonomic ganglion cells The yellow lipoid pigment appears earlier than the darker pigment After dark pigment is present, both may occur in the same ganglion cells, but as ag

advances the dark pigment becomes predominant, particularly in heavily pigmented cells

The distribution of pigment within the ganglion cells varies within a wide range (Fig 82) In many of the cells, dark pigment occurs only in a narrow peripheral zone In others, it is aggregated in a restricted portion of the cell body at the base of a dendrite or the axon In occasional cells, it appears as a cap-shaped mass at the periphery of the nucleus In certain cells, masses of pigment granules also occur occasionally in the cytoplasmic processes Extracellular pigment granules also occur, particularly in ganglia in which most of the ganglion cells are heavily pigmented Under certain conditions, *e g*, in cachexia and arsenic poisoning pigment may be distributed quite uniformly throughout the cytoplasm and become so dense that the nucleus is obscured

Not infrequently, preparations of autonomic ganglia in which many of the ganglion cells contain a moderate amount of melanotic pigment exhibit no other evidence of pathologic changes This may be regarded as evidence of a previous pathologic condition, involving functional depression of the cells in question, from which they have quite fully recovered In other instances even moderate pigmentation of the ganglion cells is accompanied by changes in the structure and distribution of the chromidial substance, probably indicating an existing pathologic condition of these cells Heavy pigmentation probably always is accompanied by other degenerative changes in the autonomic ganglion cells Many undoubtedly become functionless as the normal cytoplasmic constituents are replaced by pigment granules In pyridine-silver preparations of heavily pigmented ganglia many of the ganglion cells have the appearance of a compact mass of pigment granules from which no cytoplasmic processes can be traced (Fig 83) Such excessive pigmentation results in necrosis of the ganglion cells In the advanced stages of certain chronic diseases e *g*, carcinoma most of the ganglion cells in the sympathetic trunk ganglia show exceedingly heavy pigmentation and necrosis

In a study based on preparations of ganglia of the sympathetic trunks and the celiac plexus obtained in an extensive series of autopsies following death due to a wide variety of causes at ages ranging from five weeks to seventy eight years, and preparations of sympathetic ganglia removed in the surgical treatment of disease in approximately 50 patients Kuntz (1938) found melanotic pigment in some of the ganglion cells in nearly all individuals thirty years of age or over and in some in the younger age groups Some of the ganglia which fall within the age limits of eighteen to twenty five years showed moderate pigmentation in some cells but none below the age of thirty five years showed marked pigmentation The most heavily pigmented ganglia in this series are those obtained following death from carcinoma They fall within an age range of forty-six to seventy seven years In general the ganglia from the younger individuals are less heavily pigmented than those from the older but the difference is not marked except in the most extreme cases The excessive pigmentation of the autonomic ganglion cells in this group of patients undoubtedly is associated with the malignant disease

The occurrence of lipoid pigment in autonomic ganglion cells in human fetuses during the fifth and later months of intrauterine life has been reported by various investigators, including Lubimoff (1874) and de Castro

(1923) Spiegel and Adolf (1922) and Herzog (1926, 1931) reported traces of yellow pigment in the autonomic ganglion cells in the new born It is present in but small amounts in the very young and gradually increases in quantity but except in the presence of pathologic conditions it is still meagerly represented at puberty

Dark pigment (melanin) is rarely observed in the autonomic ganglion cells in the very young Herzog (1918) reported its occurrence in a child one year of age Other isolated cases of the occurrence of melanotic pigment in autonomic ganglion cells before puberty have been reported The occurrence of melanotic pigment in autonomic ganglion cells before puberty, except in minute quantities undoubtedly is associated with marked pathology

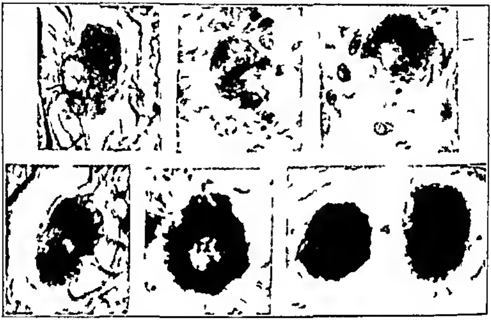


FIG 82 —Autonomic ganglion cells (human) illustrating successive stages in pigmentation

The genesis of pigment in nerve cells and the relation of the lipoid and melanotic pigments to each other have been discussed extensively Certain investigators (Pilcz 1895, Rosin, 1896, Obersteiner 1903 1909 Marinesco 1909) have regarded pigment as a normal organic constituent of certain nerve cells since it occurs so commonly in certain portions of the central nervous system in man *e g* the substantia nigra and the locus ceruleus Under normal conditions the substantia nigra contains no pigment in the lower mammals (Dolley and Guthrie 1918) Neither does it always contain pigment in man Pilcz and Marinesco both of whom traced the development of pigment in the substantia nigra in man do not agree regarding its age incidence probably due to the fact that the material studied was pathologic in varying degrees and pigment was not present at the same age in all cases If pigment is not a normal constituent of certain nerve cells in the lower mammals, it seems highly improbable that the corresponding cells in man would naturally be endowed with this apparently useless material

Lipoid and melanotic pigments commonly occur intimately intermingled in ganglion cells and sometimes in the same granules (Hueck, 1912) They

also possess certain histochemical properties in common (Hueck, 1921, Bethe and Fluck, 1937, Herzog 1938) These findings strongly suggest that they are closely related in origin They probably represent only different phases in the metabolism of the same material (Herzog 1926, 1938) Certain investigators have regarded pigment in nerve cells as a normal product because it has been observed frequently in individuals who apparently were in good health Such relatively inert material as melanotic pigment however, may be retained in the cells long after the pathologic process responsible for its origin has subsided and the cells in question have quite fully recovered The facility with which nerve cells acquire pigment seems to be correlated with the degree of differentiation of these cells The autonomic ganglion cells exhibit a relatively low degree of differentiation They also acquire pigment with relative facility

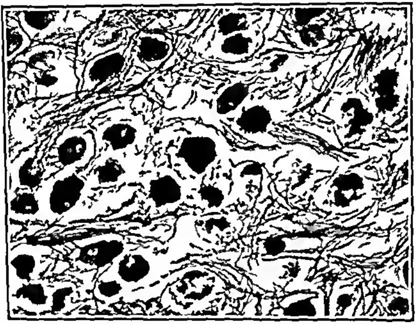


FIG 83 —Photomicrograph from a section of a sympathetic trunk ganglion obtained at autopsy following death due to carcinoma showing heavy pigmentation of ganglion cells

In an experimental study carried out on dogs and rabbits Dolley (1917) always found pigmentation of the Purkinje cells associated with chronic depression Stimulation ranging from normal activity to functional senility failed to produce pigmentation in these cells Chronic depression alone resulted in pigmentation of the Purkinke cell in the animals used In another series of experiments, carried out on fowls lipoid pigment was observed in the Purkinje cells following acute depression It should be recalled in this connection that lipoid pigment does not occur in the dog and the rabbit since their fat always is lipochrome-free In still another series of experiments carried out on dogs and rabbits, Dolley and Guthrie (1918) observed pigment in the nerve cells in various parts of the nervous system including the superior cervical sympathetic ganglion In these experiments also, pigmentation of the nerve cells was induced only by chronic functional depression They therefore, advanced the opinion that pigmentation of the nerve cells in the dog and rabbit is induced solely by functional depression

The genesis of pigment in nerve cells probably is essentially similar to its genesis in various other cells. The derivation of pigment from intranuclear and extranuclear chromatin has been described repeatedly. Hertwig (1904) reported the transformation of extranuclear chromatin into pigment in *Actinosphaerium eichhorni* while in a state of functional depression. The depressed cells were in a condition of hyperchromatism, consequently, the transformation of chromidial material into pigment, under these conditions may be regarded as a phenomenon of reorganization necessary for the restoration of the nucleus-plasma balance. Howard (1908) confirmed Hertwig's findings in the same species under similar conditions. He also observed the transformation of chromatin into pigment within the hypertrophied and hyperchromatic nucleus. Rössle (1904) reported the extrusion of nuclear material and its transformation into pigment in the cytoplasm in cells of a melanosarcoma. Howard and Schultz (1911) also reported the occasional transformation of chromidial substance into pigment in tumors derived from unpigmented cells. In the dermal chromatophores of various animals, according to Schultz (1912) the process of pigmentation begins in the undifferentiated mesoblastic cell by the extrusion of chromatin from the nucleus into the cytoplasm resulting in the formation of a functional chromidial net. The chromidial substance in the cytoplasm later becomes transformed into pigment.

According to Dolley (1917) and Dolley and Guthrie (1918), the formation of pigment in the nerve cells in experimental animals in a state of functional depression involves both the intranuclear and extranuclear chromidial apparatus. They observed the transformation of chromidial material into pigment both in the nucleus and the cytoplasm. Their findings, in the animals used (dog, rabbit), strongly suggest that melanotic pigment arises in the nerve cells only from the chromidial substance under the influence of chronic functional depression.

Species whose tissue fat is colored with the carotinoids (cow, horse, fowl, man, etc), carry the carotinoid pigments in the blood plasma. Fat absorbed by the cells in these species may carry in carotinoid pigment. Since nerve cells, like other tissue elements, absorb fat, the occurrence of lipoid pigments in them could be explained on this basis. The fact that lipoid pigment has been observed often in nerve cells, particularly in the young, strongly suggests that it may exist in these cells under normal physiologic conditions. That its accumulation in the nerve cells is facilitated under certain pathologic conditions is amply demonstrated. Dolley and Guthrie also advanced certain experimental data which indicate quite clearly that excessive deposition of fat in the nerve cells is a characteristic of functional depression.

Vacuolization.—The occurrence of vacuoles in occasional ganglion cells in sections of autonomic ganglia prepared by the usual methods need not be regarded as abnormal (Fig. 84, *A*). Vacuolization of ganglion cells in large numbers usually is associated with other degenerative changes in the cells and must be regarded as pathologic. In some instances, small vacuoles occur which are separated from one another only by thin protoplasmic septa. The latter condition was observed by Spiegel and Adolf (1922) in a case of pemphigus vegetans. This observation is of especial interest since the spinal ganglion cells undergo similar vacuolization in this disease. Vacuolization of the autonomic ganglion cells also has been observed in

cases of advanced arteriosclerosis (Spiegel and Adolf, 1922, Stümmler, 1923) and other chronic pathologic conditions (Kuntz 1934 1938) Not uncommonly vacuolated cells also contain pigment but no essential relationship of the vacuoles to the pigment has been pointed out Many of the vacuoles apparent in sections of fixed material probably represent intracellular fatty inclusions

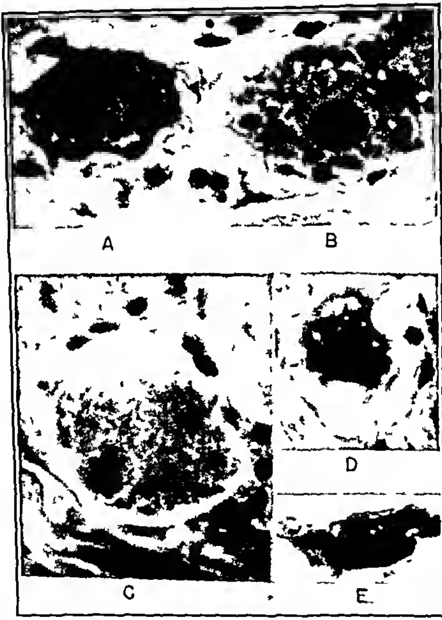


Fig 84 —Photomicrographs of sympathetic ganglion cells (human) showing pathologic alterations *A* vacuolization *B* early neuronophagia *C* hydropic enlargement *D* shrinkage with vacuolization *E* shrinkage with partial chromatolysis

In some instances large vacuoles are formed through confluence of smaller ones A single giant vacuole may occupy the major portion of the cell body, crowding the nucleus toward one pole (de Castro, 1931) Some vacuolated ganglion cells are characterized by enormous swelling of the cell body causing distention of the cell capsule Ganglion cells in this condition usually show evidence of neurofibrillar degeneration

Neuronophagia —Neuronophagia of autonomic ganglion cells may occur either as a primary or a secondary process. Primary neuronophagia is brought about mainly by inflammatory infiltration which also affects the ganglion cell capsule, secondary neuronophagia by changes in the ganglion cells which result in a chemotactic attraction of phagocytic elements. Only secondary neuronophagia can take place under physiologic conditions. Destruction of occasional autonomic ganglion cells by this process need not be regarded as abnormal, particularly after middle age. Empty cell capsules and capsules which contain only a remnant of the ganglion cell may be observed occasionally in preparations of autonomic ganglia which show little or no evidence of other pathologic changes. Not infrequently, preparations of autonomic ganglia in which most of the ganglion cells are pigmented and exhibit changes in the chromidial substance also exhibit evidence of extensive neuronophagia. The destruction of the ganglion cells by secondary neuronophagia may be accomplished by cells derived from the lining of the ganglion cell capsule or by wandering phagocytic elements, usually small round cells, which are attracted into the cell capsule, depending on the type of metabolic disturbance in the ganglion cell.

Primary neuronophagia of autonomic ganglion cells is commonly associated with inflammation of the autonomic ganglia. In the initial stages of inflammation the cells lining the ganglion cell capsules proliferate and the walls of the capsules become materially thickened. Some of the cells become separated from the wall of the capsule and lie free in the lumen where they assume the role of phagocytes and take part in the destruction of the ganglion cell. Inflammation of the autonomic ganglion results in its infiltration by lymphocytes and leukocytes. Some of these cells also penetrate the ganglion cell capsules and take part in the phagocytosis of the ganglion cells (Fig. 81 *B*). The phagocytic process may continue until the ganglion cell is completely consumed. After the inflammatory process has subsided, nothing remains in the lumen of the thickened capsule, in such cases, but amorphous material, colloidal masses and fragmented cells (Stammler, 1923).

According to Spiegel and Adolf (1922), neuronophagia, particularly the secondary type, is a more common phenomenon in the autonomic ganglia than in the central nervous system. This difference probably is correlated with the difference in the relationships of the neurons in the autonomic ganglia and the central nervous system, respectively, to the adjacent tissue. The neurons in the central nervous system are protected against the injurious effects of metabolic disturbances due to the important role of the neuroglia cells in the removal of injurious metabolites from them. The cells lining the ganglion cell capsules do not protect the autonomic ganglion cells in the same manner (Spiegel and Adolf, 1922).

Hyaline Degeneration —Under certain conditions hyaline degeneration in autonomic ganglion cells is not uncommon. Herzog (1926) reported eosinophilic hyaline bodies in the cytoplasm in many of the autonomic ganglion cells in cases of paralysis agitans and chronic morphinism. Onuma (1929) reported similar bodies in autonomic ganglion cells in cases of poisoning with sulphuric acid. Grunberg (1930) reported hyaline changes in autonomic ganglion cells in experimental animals subjected to chronic lead poisoning. In his preparations, the major portion of the cytoplasm appears

uniformly pale and agranular in many of the cells The cell body is somewhat swollen and the nucleus is displaced toward the periphery In some instances it actually protrudes at the surface

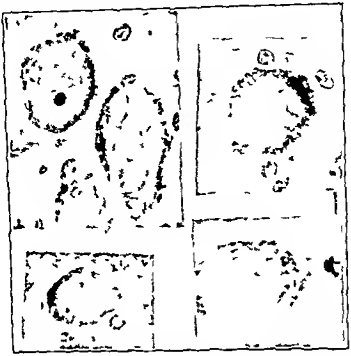


FIG 85 — Autonomic ganglion cells (human) showing hyaline degeneration

Hydropic Alteration —Hydropic alteration of autonomic ganglion cells as described by de Castro (1931) is characterized by marked enlargement of the cell body acquisition of globular form and degenerative changes in the neurofibrillar structure which suggest pathologic coagulation of the neurofibrillar substance rather than hypertrophy of the neurofibrils (Fig 84 C) The central portion of the cell body is made up of polyhedral alveoli which appear to be filled with amorphous matter which may include argentophile concretions The entire cell body appears pale due to diminution of the chromidial substance The nucleus is large and vesicular The dendrites usually show hypertrophy of the neurofibrils particularly at the surface, and a clear central core They may also show vacuoles and argentophile concretions Hydropic alteration may be observed in some ganglion cells in a wide variety of pathologic conditions including chronic alcoholism (de Castro 1931) chronic polyarthritis and advanced carcinoma (Kuntz 1938)

Shrinkage —Shrinkage of autonomic ganglion cells is a common phenomenon in various pathologic conditions, particularly senility and cachectic states Shrunken cells, in these conditions, usually also exhibit other pathologic changes *e g* chromatolysis and pigmentation The most heavily pigmented cells not uncommonly are shrunken to a relatively small mass Shrunken ganglion cells which contain no pigment frequently also exhibit displacement of the nucleus toward the periphery and other nuclear changes In some instances the nucleus actually is extruded from the cell

Preparations of apparently normal ganglia not uncommonly exhibit some shrunken ganglion cells which stain intensely, particularly after

formalin fixation (Fig 84, L) Both the cytoplasm and the nucleus appear hyperchromatic, but the chromidial substance in the cytoplasm does not exhibit discrete granules This staining reaction according to Onuma (1929), is determined by the oxygen content of the cell and need not be regarded as indicative of a pathologic state It probably indicates a particular phase of cell activity

Neurofibrillar Changes —Most of the histopathologic changes in autonomic ganglion cells described above involve changes in the neurofibrillar structure in some degree The retrogressive changes following injury to the axon or its complete interruption sometimes involve hypertrophy of the neurofibrillar structure particularly in the perinuclear zone (Lawrentjew, 1925, de Castro 1929) and hyalinization of the peripheral cytoplasm with or without neurofibrillar hypertrophy (de Castro 1931) Hypertrophy and coalescence of the neurofibrils in some of the ganglion cells has been reported in certain diseases, particularly hydrophobia and tabes (de Castro 1929) The interpretation of observed neurofibrillar changes is particularly difficult because the appearance of the neurofibrillar structure in sections is determined largely by the fixation and the staining technic employed Not infrequently modifications in the neurofibrillar network represent artifacts

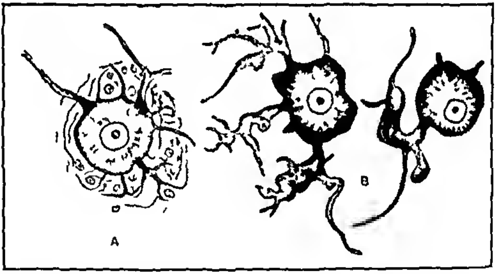


Fig 86 —Ganglion cells drawn from silver preparations of sympathetic ganglia (human age seventy-eight years) showing (A) development of short accessory dendrites and (B) irregular hypertrophy of dendrites

Dendritic Modifications —Budding and hypertrophy of the dendrites of some ganglion cells occurs not uncommonly particularly in advanced age Short dendrites not infrequently present a tuberose or beaded appearance and terminate in club shaped enlargements Longer dendrites frequently exhibit irregular local thickenings by virtue of which they appear highly distorted (Fig 86, B) In some instances dendrites give rise to new processes of variable length and caliber which form one or more complex brushes or tracts (Fig 87, A and B) Structures of this kind have been reported by de Castro (1931) particularly in cases of tabes alcoholism and multiple sclerosis and by Kuntz (1938) in cases of advanced carcinoma and senility

New dendritic processes may arise relatively late Some investigators, particularly de Castro (1918, 1923) and Levi (1925), have supported the assumption that autonomic ganglion cells may undergo continuous differentiation throughout life More or less elaborate pericellular dendritic nests are not uncommon particularly after the age of forty They may include terminal branches of dendrites of adjacent ganglion cells or only dendrites of the same cells which have grown relatively long and, branching profusely, form a dense fibrous structure around the cell body (Fig 87, C

Fig 87 —Photomicrographs of ganglion cells (human age seventy-eight years) showing (A) hypertrophy of dendrites (B) dendritic brush and (C and D) pericellular dendritic nests

and D) In the more elaborate dendritic nests the terminal branches of the dendrites resemble the terminal branches of axons In the simpler ones formed by the terminal branches of dendrites of adjacent ganglion cells the processes involved retain their typical dendritic appearance In some instances numerous short dendrites which do not penetrate the ganglion cell capsule undergo anastomosis, thus giving rise to simple or complex fenestrations

Changes in the Interstitial Tissue —Preparations of autonomic ganglia taken from new-born or young children contain relatively little interstitial

connective tissue, consequently, the ganglion cells are closely aggregated, their capsules being separated only by a delicate connective tissue framework. Some of the cell capsules are separated somewhat farther by bundles of nerve fibers. Preparations of autonomic ganglia taken from persons of middle age and older, in the absence of marked pathologic changes show a progressive increase in the amount of interstitial connective tissue but in most cases it does not become excessive. In the presence of pathologic conditions which are accompanied by marked changes in the autonomic ganglion cells the interstitial connective tissue usually also shows a marked increase. For example, in cases of senility with cachexia the interstitial connective tissue becomes so excessive that most of the ganglion cell capsules are separated widely from one another. In cases of arteriosclerosis the autonomic ganglia exhibit excessive development of the interstitial connective tissue and marked thickening of the adventitia of the arteries and veins (Staemmler, 1923). As the interstitial connective tissue increases new capillary blood vessels also arise. The findings in preparations of autonomic ganglia taken at autopsy in a wide variety of cases strongly suggest that all chronic pathologic conditions which involve marked changes in the autonomic ganglion cells are accompanied by an abnormal increase in the interstitial connective tissue. Chronic infections and other conditions which result in inflammation of the autonomic ganglia also result in hyperplasia of the interstitial connective tissue. In a study of 100 cases following infectious diseases Laignel-Lavastine (1905) observed hyperplasia of the interstitial connective tissue in all in which the infection had run a chronic course. Staemmler (1923) reported pathologic changes in the interstitial connective tissue in the autonomic ganglia in approximately 30 cases in which death resulted from infectious disease. Kuntz (1934) observed hyperplasia of the interstitial connective tissue in the preparations of most of the sympathetic ganglia in an extensive series removed by operation in cases of chronic arthritis, Raynaud's disease and thrombo-angiitis obliterans.

Hyperemia and infiltration of autonomic ganglia under pathologic conditions, even in the absence of infection, is a common phenomenon (Staemmler, 1923). Infiltration of the interstitial connective tissue in certain of the autonomic ganglia in senility and cachectic states was observed by Lor as early as 1874 and more recently by various investigators (Spiegel and Adolf, 1922; Staemmler, 1923; Herzog, 1931; Kuntz, 1938). These phenomena also have been reported in cases of chronic arthritis, Raynaud's disease and certain other chronic states (Kuntz, 1934). The exact sources of the infiltrating cells as yet are not definitely known. These cells are identical in their staining reactions with lymphocytes and frequently are more closely aggregated in proximity to the blood vessels than throughout the interstitial tissue (Spiegel and Adolf, 1922; Kuntz, 1934). These facts strongly suggest that they invade the tissue from the blood vessels but do not prove their hematogenous origin. Regardless of their origin they must be regarded as wandering phagocytes which in many instances invade the ganglion cell capsules and take part in the phagocytic destruction of the ganglion cells. In the absence of infection this process must be regarded as secondary neuronophagia. Spiegel and Adolf (1922) observed that many of the wandering cells in proximity of the blood vessels were laden with fat. This observation

supports the theory that the wandering elements in question are phagocytes and indicates quite clearly that they take part in the transportation of waste metabolites toward the blood vessels, thus facilitating their elimination through the blood stream

Preparations of autonomic ganglia taken in cases of infectious disease, if not complicated by the changes described above present quite a different histologic picture There may be but little increase in the interstitial connective tissue or none but, in many cases in which marked changes in the ganglion cells as yet are not apparent there may be marked capillary hyperemia According to Stammler hyperemia of the autonomic ganglia in cases of infection commonly is accompanied by abundant diapedesis of white cells which become aggregated in the perivascular lymph vessels and gradually invade the interstitial tissue throughout the ganglion Under these conditions the invading cells are mainly lymphocytes and mononuclear leukocytes Although neuronophagia may be evident lymphocytes and leukocytes are not commonly found in large numbers within the ganglion cell capsules Phagocytic destruction of autonomic ganglion cells is observed only rarely in cases of acute infection

Although acute infectious diseases result in inflammatory reactions of the blood vessels and connective tissue framework of the autonomic ganglia and retrogressive changes in the ganglion cells which in some instances result in necrosis of many of these cells the infecting organisms are rarely observed in the autonomic ganglia In preparations taken from a wide variety of infectious cases Stammler (1923) observed bacterial organisms in the autonomic ganglia in but a single case *viz* a case of streptococcus septicemia He therefore concluded that the primary degenerative changes in the autonomic ganglion cells represent reactions to toxic substance and that these reactions call forth secondary inflammatory reactions in the ganglia

This point of view is supported by certain data reported by Fischer and Kaiserling (1939) In their experiments on rabbits, lymphangitis and adenitis induced by serum injections in the lymphatics of the pelvic viscera was accompanied by inflammation of the ganglia of the sympathetic trunks Injection of sterile antigens into the lymphatics of the liver and gall bladder which resulted in local inflammation also resulted in inflammation of the celiac ganglia Their findings not only demonstrate the capacity of noninfective toxic substances to produce sympatheticoganglionitis but also emphasize the importance of the lymphatics in the extension of inflammatory processes from focal areas to adjacent autonomic ganglia Disturbances of autonomic function associated with endometritis lymphadenitis pancreatitis etc in many cases undoubtedly can be explained on this basis

Modifications of Ganglion Cell Capsules — The pathologic changes in autonomic ganglia not infrequently include thickening of some of the ganglion cell capsules and hyperplasia of the lining cells The thickening involves mainly the non-cellular membranous portion in contact with which the lining cells rest As the lining cells increase in number they become more prominent and some of them no longer lie in contact with the membranous layer of the capsule Some appear to be detached from the lining of the capsule and lie in contact with the ganglion cell body causing slight indentations in its cytoplasm Most of the cells within the capsule

placement of the distal segment of the nerve. Experimental findings of certain other investigators do not support this point of view. Data reported by Tower and Richter (1931) and Hinsey, Phillips and Hare (1940) fail to indicate appreciable regeneration of interrupted postganglionic fibers. Kirgis and Obler (1944) reported regrowth of postganglionic sympathetic fibers in cats following their interruption but failed by physiologic tests to demonstrate reestablishment of functional connections within a postoperative period of three hundred days.

Relation of Autonomic Lesions to Disease.—Statement of the Problem.— The data set forth above show clearly that many pathologic conditions including both acute and chronic infectious diseases and non-infectious intoxications are commonly accompanied by changes in the autonomic ganglia and more particularly in the autonomic ganglion cells which must also be regarded as pathologic. The question naturally arises: are the pathologic changes in the autonomic ganglia merely accompaniments of disease processes brought about by the same causes which gave rise to the disease in question or is there a causal relationship between the disease process and the accompanying pathologic changes in the autonomic ganglion cells? The further question also arises: may not pathologic changes in the autonomic ganglion cells which are either induced by a disease process or arise simultaneously with it become causative factors in the production of other simultaneous or subsequent pathologic processes? These questions are of far reaching importance both physiologically and clinically but the data available at present do not afford an adequate basis for their solution in all cases.

Criteria of Variations Related to Age and Variations Related to Disease.— In a study based on preparations of ganglia obtained in an extensive series of autopsies following death at ages ranging from five weeks to seventy-eight years and ganglia removed in the surgical treatment of disease in approximately 50 patients ranging in age from six to seventy-one years, Kuntz (1938) pointed out that preparations of ganglia within any given age group exhibit certain variations common to all the ganglia in that group but the ganglia of certain individuals in every age group exhibit a wider range of variation than others. Certain variations appear in some cases which are not common to all in the same age group while certain of the common variations appear in exaggerated form. The ganglia in every age group which exhibit only those variations which are common to all ganglia within that group undoubtedly may be regarded as most nearly normal. These common variations, consequently, are related to age. Variations which appear in some of the ganglia in a given age group and not in others obviously depend on factors other than age. Some of these variations undoubtedly are pathologic in some degree. The appearance in exaggerated form of variations common to all the ganglia in the same age group probably is causally related to pathologic lesions in the body which at least results in modifications of metabolic functions.

According to these criteria, variations in autonomic ganglia which may be regarded as related to age include (1) growth and differentiation of the ganglion cells to maturity, (2) development of secondary dendrites and other dendritic modifications in some of the ganglion cells during adult life, (3) deposition of pigment in moderate amounts in some of the ganglion cells particularly after the age of thirty to thirty-five years, (4) depletion of the

chromidial substance in some of the ganglion cells (5) degenerative changes in occasional ganglion cells particularly in advanced age including hydropic enlargement vacuolization neuronophagia in moderate degree and necrosis, (6) moderate progressive increase in the quantity of interstitial connective tissue from birth to advanced age and (7) thickening of the ganglion cell capsules in some degree and the occasional occurrence of free cells within the capsules Variations which may be regarded as pathologic include (1) elaborate development of dendritic nests dendritic brushes etc and excessive budding and hypertrophy of dendrites (2) marked changes in the chromidial structure in large numbers of ganglion cells including hypochromatism in some cells and hyperchromatism in others, (3) excessive pigmentation of ganglion cells (4) marked degenerative changes in relatively large numbers of ganglion cells particularly in the less advanced age groups including hydropic enlargement vacuolization hyalinization neuronophagia and necrosis (5) hyperemia and infiltration of the interstitial tissue and hyperplasia of both connective tissue and non connective tissue elements and (6) marked thickening of ganglion cell capsules with proliferation of the lining cells

The histologic variations in autonomic ganglia which are related to disease like those which are related to age fall into certain general categories consequently their relation to particular disease processes in individual cases may not be apparent Craig and Kernohan (1933) described the variations observed in the most extensive series of sympathetic ganglia removed surgically which has been available for study including ganglia removed in the treatment of Raynaud s disease thrombo-angiitis obliterans chronic infectious arthritis sclerodermia etc They have regarded the histologic findings in this series as within the limits of normal variation Their criterion of normal histologic variation has been based on a study of preparations of sympathetic ganglia taken at autopsy in 40 consecutive cases following death due to various causes excluding the diseases in the treatment of which the ganglia in their surgical series have been removed

In view of the criteria of variations related to disease outlined above the establishment of a norm on the basis of observations on preparations of human ganglia obtained at autopsy must be regarded as hazardous because of the effects of pathologic conditions either preceding or associated with the cause of death which may have exerted an influence on the sympathetic ganglia and ganglion cells

In a study of a somewhat similar but less extensive series of sympathetic ganglia removed surgically Kuntz (1934) using a criterion of normal variation based on a study of preparations of ganglia obtained from normal animals reported histologic variations which could not be regarded as falling within the normal range Of these the most significant include marked infiltration of the interstitial tissue diminution of the chromidial substance in a large percentage of the ganglion cells hydropic enlargement of a small number vacuolization and hyaline degeneration of an appreciable number and neuronophagia of relatively few Some of these variations obviously are related to disease but since those observed in the various cases fall into the same general categories those observed in a particular individual case cannot be regarded as specifically related to the disease process in question

Histopathologic Changes in Autonomic Ganglia Associated with Specific Pathologic Lesions.—As pointed out in the preceding pages, all of the more marked histopathologic changes observed in autonomic ganglia have been reported in patients with chronic disease. Inflammation of autonomic ganglia in some degree is not uncommon in acute disease, particularly acute infectious disease. Excessive pigmentation and necrosis of ganglion cells not uncommonly are associated with advanced carcinoma and cachectic states. Changes in the chromidial structure and other cytoplasmic variations in ganglion cells and infiltration of the interstitial tissue in some degree have been reported in a wide variety of pathologic conditions. Significant data regarding specific changes in the autonomic ganglia associated with specific diseases are not forthcoming.

Histopathologic changes in the autonomic ganglia induced experimentally in animals fall into the same general categories as those observed in human material. Tomazawa (1931) reported changes in the chromidial structure, displacement of the nucleus toward the periphery and vacuolization of the cytoplasm in many ganglion cells in the superior cervical and other sympathetic trunk ganglia and complete degeneration of some ganglion cells in dogs following ligation of the common bile duct or injection of bile acids. Burns, Heese and Sellmann (1937) reported extensive nonspecific changes in the autonomic ganglion cells in cats deprived of their adrenal glands long enough to bring about classical signs of adrenal insufficiency. The degenerative changes in the ganglion cells varied in degree directly with the severity of the adrenal deficiency as indicated by the physical signs. A causal relationship of the ganglion cell changes to adrenal insufficiency is obvious in these experiments, but the mechanism through which the ganglion cells are affected is not apparent.

General Effect of Autonomic Lesions on the Course of the Associated Disease.—Histopathologic changes in the autonomic ganglia and ganglion cells which are associated with disease may be induced by the cause of the disease or arise as a result of the disease process. The pathologic changes which arise in the autonomic ganglia and ganglion cells during the course of an infectious disease obviously must be regarded as a result of the disease process. They are referable mainly to the direct effect of intoxication and metabolic disturbances, including inflammatory reactions. In many cases they play an important role in the course and termination of the disease due to their stimulating or depressing effect on the nerves through which the regulatory nervous control of the visceral functions is mediated. For example, continued stimulation of the sympathetic or depression of the parasympathetic innervation of the gastro-intestinal canal results in chronic constipation. On the contrary, depression of the sympathetic or stimulation of the parasympathetic innervation of the stomach and intestine results in hypermotility of the gastro-intestinal musculature.

Not a few investigators have called attention to the clinical importance of the effect on the vasomotor apparatus of changes in the sympathetic ganglion cells brought about during the course of infectious diseases. On the basis of extensive histologic data, particularly the results of Mogilnizcky's (1923) studies bearing on the relation of pathologic changes in the autonomic ganglia to infectious diseases, Abrikossoff (1923) pointed out that those infectious diseases in which the symptoms referable to

depression of the vasomotor apparatus are most marked also are accompanied by the most marked degenerative changes in the autonomic ganglion cells. On the other hand, certain infectious diseases usually are not accompanied by marked vasomotor disturbances even though many of the autonomic ganglion cells undergo pathologic changes.

Chronic infections as well as repeated acute infections and other forms of intoxication invariably result in necrosis of many autonomic ganglion cells and less extensive damage to others, resulting in impairment of function of the autonomic nervous system in a greater or lessder degree. Although it must be assumed that the autonomic ganglion cells possess the capacity for recuperation within relatively wide limits, it is not inconceivable that even moderate pathologic changes in these cells may result in changes in their reactivity of relatively long duration. Many visceral neuroses undoubtedly have their origin in functional impairment of the autonomic nervous system. The finding by D'Amato and Marci (1905) of chronic parenchymatous and interstitial inflammation of the enteric ganglia in cases of gastritis is in full accord with this assumption. On the basis of extensive clinical studies, Laignel-Lavastine also expressed the opinion that many of the neuroses of the gastro intestinal canal have their histopathologic substratum in impairment of the autonomic nervous system. A significant role of lesions of the autonomic nervous system in the genesis of arteriosclerosis also is indicated by extensive clinical and experimental findings (Stammler 1923, Danisch 1928, and others). The common occurrence in sympathetic ganglia removed surgically in the treatment of chronic polyarthritis, Raynaud's disease and other peripheral vascular diseases of histologic changes indicative of hyperactivity of the ganglion cells (Kuntz 1934) supports the assumption that, irrespective of its cause, peripheral vasomotor hyperactivity is a significant factor in the progress of diseases characterized by vascular hypertonus, particularly in the extremities.

Neoplasms.—True nerve tumors, *i. e.*, neoplasms which consist of nervous tissue elements, occur relatively infrequently but are more common in the autonomic than in the central nervous system. They also are more common in the sympathetic than in the parasympathetic division. Neoplasms of the autonomic system include both benign and malignant tumors but their clinical manifestations are not well known. In most of the cases reported, the neoplasm was not recognized clinically but was discovered at autopsy and usually regarded as a purely secondary finding. Malignant neoplasms of the autonomic nervous system occur almost exclusively in infants and young children. The symptoms most commonly associated with them, according to Stern and Newns (1937), are pain in the lower extremities, swelling of the abdomen and periodic fever. Benign tumors of the autonomic system may occur at any age. The fact that they usually are not recognized clinically suggests that they exist without giving rise to marked symptoms. In most cases, neither the patient nor the physician is aware of their presence. Symptoms referable to a benign tumor of the autonomic system are due mainly to the mechanical effects of the tumor mass. In some cases they may warrant surgical interference.

Neoplasms of the autonomic nervous system may be classified as (1) neurocytomata, (2) neuroblastomata, (3) sympathoblastomata, (4) ganglioneuromata, (5) paragangliomata and (6) neurofibromata, all of which are

closely related ontogenetically All the cellular types not only merge almost imperceptibly into one another but cells in all stages of development also may occur in the same tumor Neurofibromatosis may be combined with any of the other types of tumor formation

Neurocytoma — The neurocytoma consists mainly of undifferentiated cells of nervous origin Marchand (1907) reported a tumor of this type in a man aged fifty-six years which he described as a neurocytoma of the Gasserian ganglion According to his account it was composed of undifferentiated round, oval or polygonal cells with homogeneous cytoplasm and a large vesicular nucleus No fibrillar structure was apparent in the ground substance Wright (1910) pointed out that the cells composing neoplasms of this type are neurocytes in the undifferentiated stage In some instances the ground substance reveals delicate fibrils which react to Mallory s stain neither like neuroglia, collagenous fibers nor fibroglia but resemble the fibrils which occur in the primordia of the autonomic nervous system Both the cells and fibrils in the tumor exhibit the same morphological characters and arrangement as the cells and fibrils in the autonomic primordia and adrenal medulla The fibrils tend to run in parallel bundles with which characteristic aggregates of cells are associated Preparations of these tumors exhibit ball like structures composed of two or three concentric rows of nuclei surrounding a central meshwork of delicate fibrils which conform to the rosettes described by Kuster (1905) in preparations of neuroblastomata but are not morphologically identical with the rosettes which are characteristic of the glioma Inasmuch as undifferentiated cells of nervous origin (indifferent cells) migrate from all parts of the central nervous system Wright (1910) advanced the opinion that neurocytomata may occur in any part of the body Having himself recognized four tumors of this type in a single year he also concluded that neurocytomata occur more frequently than is indicated by the number of reported cases

Neuroblastoma — The neuroblastoma is a malignant neoplasm which may involve any part of the nervous system It occurs most frequently at the site of a sympathetic ganglion in the adrenal medulla or elsewhere behind the peritoneum whence it commonly metastasizes to the liver skeletal system and lymph nodes Of 40 cases reported by Lewis and Geschikter (1934) the primary tumor was located in the adrenal medulla or an adjacent sympathetic ganglion in 33 It is composed mainly of neuroblasts which tend to become arranged in solid masses of fibrils (Kuster s rosettes) Fibrils usually are present in the ground substance, although some tumors of this type exhibit very little fibrillar differentiation As pointed out by Landau (1913), the fibrils only represent a degree of differentiation of the cells If the cells remain in the early phases of neuroblast differentiation fibrils scarcely are apparent and the tumors may present a histologic picture similar to that of a lymphosarcoma but if cell differentiation has advanced beyond the earliest neuroblast stages the fibrils are more numerous In general, the degree of differentiation of the cells in these tumors is correlated with age Most of the neuroblastomata reported have occurred in infants or young children Over 80 per cent of those in Reid s (1928) series occurred in patients under two and a half years of age Meunier (1927) reported the occurrence of a typical sympathetic neuroblastoma in a girl, aged six and a half years A few neoplasms

probably of this type in adults also have been reported (Ritter, 1925, Meltzer, 1926). The younger the patient the less differentiated are the cells and the more malignant is the neoplasm. Landau emphasized the direct relation of the tissue differentiation, the character of the tumor and the age of the patient to one another. If the host survives, tissue differentiation increases with age, while malignancy decreases and the tumor assumes the appearance of a malformation. Most of the neuroblastomata of the differentiated type include cells in various stages of differentiation but either those of the undifferentiated or those of the more differentiated type predominate. Foci of indifferent cells also may be present. Differentiated cells occur, but less frequently, in the undifferentiated neuroblastomata. Indeed, neuroblastomata may exhibit any combination of differentiated and undifferentiated cells (Wahl, 1914).

The primary diagnosis of a neuroblastoma has rarely been made without a biopsy. During the early stages of the disease symptoms may be absent. Not infrequently the first evidence of the disease is due to metastases in the head, resulting in intracranial pressure with protrusion of one or both eyes, discoloration of the eyelids, profound anemia and swellings about the bones of the skull. Drowsiness, optic neuritis and blindness may follow. Boyd (1926) has called attention to the peculiar type of periosteal reaction and calcification which is associated with metastasis in the bones. This osseous lesion, as has been pointed out by Holmes and Dresser (1928), yields a characteristic roentgenogram which may be regarded as pathognomonic of the neoplasm.

Sympathoblastoma.—The sympathoblastoma represents a somewhat later stage in the differentiation of sympathetic nerve cells than the neuroblastoma. It is a malignant neoplasm, occupying a position midway between the undifferentiated neuroblastoma and the ganglioneuroma, and is composed mainly of cells which have become differentiated beyond the neuroblast stage. Martius (1913) described a neoplasm of this type in the cervical sympathetic of a boy aged two and a half years. Scott, Oliver and Oliver (1933) reported 4 cases from their own laboratory and 128 cases collected from the literature in which sympathoblastomas had their origin in the adrenal medulla. Tumors of this type, according to Chandler and Norcross (1940), are relatively rare but may occur in various locations and give rise to a multiplicity of symptoms. In general those in the younger patients are less differentiated and more malignant than those in the older ones.

Ganglioneuroma.—The ganglioneuroma represents a later stage in the differentiation of nerve cells. It consists mainly of ganglion cells and fibers. The ganglion cells exhibit a wide range of variation both in size and general morphology. Many of them are relatively small round cells which, in their general appearance, have little in common with normal ganglion cells. Their nervous origin is indicated by the vesicular character and meager chromatin content of the nucleus and the character and arrangement of the chromidial bodies in the cytoplasm (Oberndorfer, 1907, Pick and Bielschowsky, 1912). The larger cells show all the characters of ganglion cells. Many of them are binuclear or polymorphonuclear. Degenerative changes in the cytoplasm are not uncommon. Many of the cells also contain pigment. According to Oberndorfer, the ganglion cells are not enclosed in capsules. Others have described ganglion cell capsules in

some instances. Many of the ganglion cells show multiple processes in
which, as well as in the cell body, neurofibrils can be demonstrated partic
ularly by silver impregnation methods. Pericellular meshworks of fibers
also have been observed (Fuchs 1921). The fibrous components of the
tumor include both myelinated and nonmyelinated nerve fibers but the
latter usually predominate. The myelinated fibers not infrequently show
evidence of degeneration. The myelin sheath may be fragmented or it may
show varicose swelling. Neurilemmal cells may be numerous. As a rule
these tumors are solitary and benign. In certain cases they are multiple
and malignant. The solitary tumors usually are definitely delimited and
do not infiltrate or metastasize. Malignancy probably depends on the
inclusion of groups of immature or undifferentiated cells. In such cases
infiltration and metastasis may take place (Miller 1908, Jacobsthal 1909
Berner, 1922). The growth of these tumors usually is slow (Sato, 1912)
but they may attain relatively large size. In some of the reported cases
the tumor was as large as a child's head or larger (Borst 1902, Olse 1906,
Braun 1912, Krecke 1915, Brunner 1921). Malignant ganglioneuromata
have been reported mainly in young persons. The younger the patient the
more undifferentiated are the cells and the more apt is the tumor to become
malignant (Falk 1907). Tumors of this type occur more frequently in
females than in males. They may occur at any age but are most common
in children and young adults and are rarely found after the age of forty
years. They have been reported in still born fetuses and new born children.
Of 98 cases reported by McFarland and Sappington (1935) 33 were under
ten years of age and 5 over sixty years. In Reid's (1930) series the young
est patient was four years of age, the oldest seventy-five. The average
age in 52 cases was nineteen years.

Paraganglioma.—The paraganglioma represents the most common
tumor of the autonomic system (Lewis and Geschickter 1934) and exhibits
many variations. It usually is benign but becomes malignant in some
cases. Being composed mainly of chromaffine tissue it may occur wherever
such tissue exists but is found most commonly in the carotid body, the
appendix and the small intestine. Paragangliomata in the adrenal medulla
are relatively rare (Reid 1930), but over 50 cases have been reported.
Since the chromaffin tissue arises from cells which become displaced from
the central nervous system with the cells which give rise to the sympathetic
primordia, the paraganglioma is genetically related to the other neoplasms
of the autonomic system. These tumors are relatively small and as a rule
are discovered in middle aged and elderly persons, being found sometimes
accidentally at autopsy. Not infrequently they are associated with neuro-
fibromatosis. Inasmuch as the cells composing the paraganglioma represent
fairly mature chromaffine cells, this tumor corresponds to the ganglio-
neuroma.

Tumors made up of immature chromaffine cells are unknown, but most
paragangliomata exhibit a wide range in the degree of differentiation of the
chromaffine cells. Most of the cells are large epithelioid elements which
often contain adrenin and glycogen. Many of them assume a character
istic brown color after fixation with chrome salts. Those which do not
react to chrome salts in this manner probably are not fully differentiated.
Although these tumors are made up mainly of chromaffine cells which appear
as polymorphous or polyhedral elements with finely granular vacuolated

cytoplasm, transitional forms, multinucleated giant cells, ganglion cells and cystic or hemorrhagic areas are often observed. Myelinated or unmyelinated nerve fibers also are encountered occasionally (Herxheimer, 1914).

Neurofibromatosis.—Neurofibromatosis involves mainly the peripheral nerves. It is frequently characterized by the appearance of multiple tumors in the subcutaneous tissue, areas of pigmentation, and less often by a condition resembling elephantiasis (elephantiasis neuromatosa). According to von Recklinghausen's original concept these tumors are derived exclusively from the perineurium and endoneurium. Verocay (1908) and others, however, have shown that in certain cases neurofibromatous growths exhibit very little connective tissue but are made up mainly of nerve fibers. Verocay assumed that the newly formed nerve fibers are derived either from the neurilemma or undifferentiated embryonic nerve cells. Other investigators have shown that tumors of this type involve both hyperplasia of the connective tissue and new growths of nerve fibers (Fuchs, 1924).

In isolated cases neurofibromatosis has been observed in the autonomic nervous system. Askanazy (1907) described tumors between the longitudinal and circular muscles in the gastro-intestinal canal in which he found ganglion cells and nerve fibers. These tumors obviously involved the myenteric plexus. In rare instances fibromatosis of the nerves supplying the bladder and seminal vesicles also has been reported (Fuchs, 1924). Roux (1926) described neurofibromatosis involving the sympathetic fibers accompanying the arteries in the pelvic region in certain cases of sclerous and cystic degeneration of the ovaries accompanied by dysmenorrhea and other pelvic disorders. Brocher (1927) reported three cases of neurofibromatosis in the autonomic nervous system. In one of these the growth involved the myenteric plexus near the cardiac end of the stomach. In another it involved the entire left sympathetic trunk from the upper end of the common carotid artery to the promontory of the sacrum. In the third case only the thoracic portion of the left sympathetic trunk was involved. In all three cases the neurofibromata were discovered as purely secondary findings at autopsy. Kass (1932) reported a rare case of neurofibromatosis involving the bladder and the skin in a boy seven years of age. In a patient with neurofibromatosis, a woman past middle age, brought to our attention by Dr. Joseph Grindon, the disease was characterized by cutaneous and subcutaneous tumors throughout the area of distribution of the sympathetic nerves derived from the left superior cervical sympathetic ganglion and complete paralysis of the sympathetic nerves in this area. Examination of sections of the tumors showed that they were made up mainly of hyperplastic neurilemma cells. The sympathetic fibers had undergone almost complete degeneration.

Nicholaysen (1921), Askanazy (1921) and Katsurashima (1932) called attention to alterations in the nerves adjoining gastric ulcers which are not always destructive but exhibit a marked tendency toward proliferative degenerative activity. According to Okkels (1927), who carried out a detailed study of the changes in the nerves in the vicinity of gastric ulcers in an extensive series of cases, the proliferative alterations of the nerve tissue constitute a central cicatrix neuroma which may originate in the enteric plexuses or periarterial nerves. These alterations are not specific for gastric ulcer, consequently they may be regarded as secondary.

Central Autonomic Lesions

Intermediolateral Cell Column.—Degenerative changes in preganglionic neurons in the intermediolateral cell column in the corresponding segments of the spinal cord have been reported following section of communicating rami or splanchnic nerves (Laignel-Lavastine, 1903), carcinoma involving the brachial plexus (Jacobsohn, 1908) and section of the cervical sympathetic trunks (Marinesco and Parhon, 1908). Chromatolysis and other changes in preganglionic neurons in the sacral spinal cord segments also have been reported following resection of the rectum (DeBuck, 1904) and suppuration and gangrene in the pelvis (Marinesco and Parhon, 1908).

Disease of the spinal cord, e.g., tumors, cavities and inflammatory processes, may give rise to disturbances of visceral functions due to its effect on the neurons in the intermediolateral column. In cases of poliomyelitis muscular paralysis is accompanied by segmental vasomotor and sweat secretory disturbances. In this disease the inflammatory process in the spinal cord may involve the intermediolateral cell column directly, but not infrequently pathological changes also occur in the corresponding ganglia of the sympathetic trunk. In some instances syringomyelia is accompanied by scleroderma and pupillary disturbances probably due to encroachment of the spinal cord lesion on the intermediolateral cell column (Buscher, 1924).

Visceral disturbances resulting from localized lesions of the spinal cord in most instances probably are due to the effect of the lesion on the preganglionic neurons. In some instances the effect of the lesion on the preganglionic neurons may be excessive stimulation of function; in others it may be depression or complete cessation of function. Excessive preganglionic stimulation undoubtedly plays a rôle in the causation of peptic ulcers in certain cases. Burdenko (1933) reported the occurrence of peptic ulcer in three patients with spinal cord lesions which involved the intermediolateral cell column. In one of these the ulcers healed promptly following surgical removal of an intramedullary tumor extending from the fourth to the seventh thoracic segments inclusive. He also reported a case in which chronic peptic ulcer associated with chronic irritation of the celiac plexus healed following removal of a fragment of shrapnel from the celiac plexus.

Autonomic Centers in the Medulla Oblongata.—Pathologic changes in certain of the visceral nuclei in the medulla oblongata have been reported. Marinesco (1897), Molhant (1910) and Brugsch, Dresel and Lewy (1920) described changes in the neurons in the dorsal vagus nuclei following vagus section or extirpation of an organ innervated through the vagi, which they regarded as indicating retrograde degeneration of these cells due to section of their axons. Ceelen (1917) described a wide range of degenerative changes including cell necrosis in the region of the vasomotor center in the medulla oblongata in cases of chronic nephritis. On the basis of his findings in these cases he advanced the opinion that, in cases of chronic renal disease, toxic substances are thrown into the blood stream which exert a selective influence on the neurons in the vasomotor center through which they are kept in a constant state of stimulation.

In postmortem examination of the brain stem Vonderahe (1939) found diffuse hemorrhage in the dorsal motor nuclei of the vagus nerves in 7 of 14 cases of peptic ulcer. A causal relationship of this lesion to the

production of peptic ulcer is not apparent in these cases, since it was associated with other lesions in the brain stem It probably represents a secondary effect of afferent impulses arising at the site of the gastro-intestinal lesion Neurogenic factors in the causation of peptic ulcer are not precluded but in all instances, as pointed out by Vonderahe, such irritative lesions in the stomach or duodenum give rise to more or less constant afferent stimulation resulting in reflex vasodilatation in the brain stem which, in conjunction with other factors acting diffusely, may reach the stage of hemorrhage Certain associated disturbances undoubtedly are caused by the lesions in the vagus nuclei For example the marked increase in the pulse rate in certain peptic ulcer patients may result from loss of the inhibitory influence of the vagus nerves due to destruction of the cardiac neurons by the hemorrhagic lesions Autonomic imbalance with respect to other viscera may in certain cases, be explained on the same basis

Autonomic Centers in the Mesencephalon —Certain diseases which involve the mid-brain (encephalitis hemorrhage tumors) are known to give rise to pupillary disturbances These disturbances are brought about by the effect of the mid brain lesion on the preganglionic components of the oculomotor nerves but little is known regarding pathological changes in these neurons or their relationship to specific mid-brain lesions

Autonomic Centers in the Diencephalon —The diencephalic autonomic centers are located mainly in the hypothalamus Their influence in the regulation of visceral functions is exerted in part through descending pathways which conduct impulses to the visceral efferent nuclei and in part through the hypophysis and other endocrine glands Certain visceral disorders are obviously related to hypophyseal lesions but the latter in many instances are causally related to lesions of the hypothalamus The effect of hypophyseal lesions therefore cannot be properly evaluated apart from those of the hypothalamic lesions with which they are associated An account of the effects of experimental hypothalamic and hypophyseal lesions on various visceral functions is included in Chapter IV In the present connection attention will be given mainly to clinical and pathologic data

Although it is located superficially and in relation to the walls of the third ventricle clinical evidence of damage to the hypothalamus in cases of severe head injury is observed relatively infrequently Even in fatal injuries pathologic changes in the hypothalamus are not commonly observed except in conjunction with more extensive and severe damage in other parts of the brain (Vonderahe 1940)

Wounds which involve localized areas of the hypothalamus in man result in metabolic disturbances comparable to those caused by experimental lesions in the corresponding areas in animals Any injury therefore, which damages or interrupts the hypothalamico hypophyseal tract may result in profound disturbances particularly in water carbohydrate and fat metabolism Tumors of the hypothalamus may cause even more diverse disturbances including somnolence and hypo- and hyperthermia Tumors adjacent to the hypothalamus which cause direct pressure upon it or occlude the interventricular foramina or the cerebral aqueduct resulting in the accumulation of cerebrospinal fluid in the third ventricle, may produce similar disturbances

Diabetes insipidus may be caused by a lesion of the hypothalamus involving damage to the supraoptic nuclei or the hypothalamico-hypophyseal tract but it probably always involves changes in the posterior hypophyseal lobe (Fisher, Ingram and Ranson 1938). The postmortem findings in a case of diabetes insipidus of long duration, reported by Biggart (1936) included extensive atrophy of the posterior lobe of the hypophysis with degeneration of the pituicytes and infiltration of the atrophic tissue with basophil cells. The hypothalamic damage in this case was limited to the supraoptic nuclei. In certain other clinical cases reported by Biggart there was no primary hypothalamic lesion but the posterior hypophyseal lobe was invaded by a malignant tumor. Warkany and Mitchell (1939) reported a case characterized by very marked polyuria following a gunshot wound in which postmortem examination revealed the bullet lodged in the infundibulum. In all of these cases the hypothalamico-hypophyseal tract was damaged. In addition to this all showed damage to the posterior hypophyseal lobe. The histopathologic findings in the hypophysis in Biggart's case first cited above confirm the earlier findings of Fisher *et al* (1935) regarding pituicyte degeneration and infiltration of the posterior hypophyseal lobe in animals with experimentally induced diabetes insipidus.

Diabetes mellitus not infrequently is associated with a hypothalamic lesion but the available evidence does not justify the conclusion that this disease is invariably caused by a central nervous lesion. The assumptions that the paraventricular nucleus in the hypothalamus is stimulated by the presence of sugar in the blood and that such stimulation elicits increased insulin secretion in the pancreatic islets is supported by clinical and pathologic data (Vonderahe 1937). The hypothalamus therefore plays an important role in the cycle of events which constitute the phenomena of this disease. In cases in which diabetes was associated with internal hydrocephalus according to Neuner and Vonderahe (1940) the intensity of the disease appeared to vary with the intensity of the hydrocephalic pressure on diencephalic structures. Cell counts of hypothalamic nuclei carried out in their study like those previously reported by Morgan, Malone and Vonderahe (1937) in cases of diabetes indicate an appreciable reduction in the numbers of neurons.

Postmortem examination of the brain stem in cases of heat stroke as observed by Morgan and Vonderahe (1939) and Vonderahe (1940) not infrequently reveals evidence of previous injury to the hypothalamus in the form of glial scars and reduced nerve cell counts particularly in the paraventricular nucleus, the lateral nucleus of the tuber cinereum and the tubero mammillary nucleus. The losses of nerve cells in the supraoptic nuclei and the gray matter in the walls of the third ventricle in these cases were not sufficiently constant to be regarded as significant. On the basis of these findings Morgan and Vonderahe advanced the hypothesis that the larger neurons in the more anteriorly located paraventricular nucleus and the neurons in the lateral nucleus of the tuber cinereum are primarily concerned with heat elimination while the more posteriorly located tubero-mammillary nucleus and the smaller neurons in the paraventricular nucleus are primarily concerned with heat production and heat conservation. In heat stroke acceleration of heat elimination fails probably due to previous injury to the neuron aggregates which normally regulate this process, while

the heat producing mechanisms are hyperactive as suggested by the alterations observed in the tubero mammillary nucleus and the smaller neurons in the paraventricular nucleus

Histopathologic changes in the hypothalamus and other parts of the brain stem not uncommonly are associated with lesions of the abdominal viscera In a study of 28 cases with lesions in the hypothalamus or the mesencephalon or both reported by Fried (1936), 18 gave evidence of direct involvement of the autonomic nerves while 6 presented pathologic changes in the gastro-intestinal tract Conversely Vonderahe (1939) reported postmortem findings in a series of peptic ulcer cases which included multiple hemorrhage in the anterior portion of the hypothalamus, particularly the paraventricular nucleus and the gray matter in the wall of the third ventricle and in some cases the supraoptic nucleus The neurones in these areas showed varying degrees of retrograde change These lesions probably are to be regarded as secondary to the gastro-intestinal lesions, due to the reflex effects of afferent impulses arising in the latter They may nonetheless play a role in the progress and the sequelae of the visceral disease

In certain cases hypothalamic lesions undoubtedly play a role in the causation of gastro-intestinal lesions In experiments on dogs reported by Keller (1936) and Keller and D Amour (1936) lesions of the hypothalamus resulted in hemorrhagic and ulcerative lesions in the gastro-intestinal mucosa In a series of animals in which bilateral vagotomy was carried out before placing the hypothalamic lesion typical hemorrhagic states developed in the gastro-intestinal mucosa but no ulcers In another series in which the lower thoracic and abdominal portions of both sympathetic trunks had been removed prior to placing the hypothalamic lesion typical gastric and duodenal ulcers developed but no hemorrhagic states were observed These results seem to support the assumption that sympathetic overstimulation may be a factor in the causation of the hemorrhagic states whereas ulceration is favored by parasympathetic overstimulation Removal of the hypophysis exerted no apparent effect on the responses of the gastro-intestinal mucosa in these experiments Ulceration apparently was precipitated not because of the lack of hypophyseal secretion but due to some neural derangement in the hypothalamus

The infectious agents of certain diseases not infrequently reach the hypothalamus via the blood stream the olfactory and optic pathways and the meninges Viruses which extend along the nerve pathways connected with the hypothalamus according to Sabin and Olitsky (1937 1938) tend to localize in it and produce local necrosis The virus of poliomyelitis not infrequently invades the hypothalamus along these routes The hypothalamic lesion caused by this virus as pointed out by Schonholzer (1937), not infrequently result in disturbances of visceral functions including tachycardia periodic sweating urinary retention constipation etc One case reported by Schonholzer terminated with paralytic ileus Hypothalamic syndromes associated with epidemic encephalitis are not uncommon According to various investigators including von Economo (1931) and Fayes and Croll (1930) the hypothalamus is invariably involved in this disease and more extensively than any other part of the brain except the substantia nigra Inflammatory changes in the walls and floor of the third ventricle in the St Louis type of encephalitis have been reported partic-

ularly by Lowenburg and Zbinden (1936) In cases of measles complicated with encephalitis Malamud (1937) found perivascular demyelinization, glial proliferation, congestion and hemorrhage in the hypothalamus as well as alterations elsewhere in the brain The occurrence of diabetes insipidus, obesity and other hypothalamic syndromes as sequellae of encephalitis associated with scarlet fever, pertussis, diphtheria, mumps, typhoid fever, etc, emphasizes the damaging effect of the virus of this disease on the hypothalamus In a case of lymphocytic meningo-encephalitis reported by Riggs (1934–1935), cellular changes were apparent throughout the brain but most severe in the nuclei of the tuber cinereum and the medulla Histopathologic changes in the hypothalamus associated with syphilis are not uncommon In a detailed study of this division of the brain stem in cases of paresis, Raskin (1934) observed pathologic changes in all instances, including marked reduction in the number of neurons particularly in the paraventricular and supraoptic nuclei and the gray matter in the walls of the third ventricle

CHAPTER XIX

VISCERAL SENSITIVITY AND REFERRED PAIN

SENSATIONS resulting from stimuli applied at the external surface of the animal organism and impulses received through its distance receptors play a major rôle in the reactions of the organism to environmental factors and in its adjustment to the external environment as a whole. Sensations resulting from stimuli arising within the body likewise play a significant rôle in the adjustment of the organism to its internal environment. The visceral organs normally are not subjected to the stimuli which constantly play upon the surface receptors. They are relatively insensitive to these forms of stimulation. Most afferent impulses arising in the viscera do not reach the sensory level, although they play a significant rôle in reflex functional regulation and the general feeling tone. Certain visceral stimuli give rise to sensations which in some instances are more or less definitely localizable; in others diffuse.

In general, the visceral organs, including the central nervous system, are insensitive to mechanical, chemical, thermal and electrical stimulation in the ordinary sense, *i. e.*, the application of these stimuli to the visceral organs, with certain exceptions, does not give rise to sensations. On the basis of experimental and clinical observations, certain investigators, notably Lennander and Mackenzie, denied the possibility of painful sensations referable to any of the internal organs which are innervated solely through visceral nerves unless the stimulation is of such a nature that it spreads beyond the area innervated solely by the visceral nerves and affects afferent components of the somatic rami of the spinal nerves. Lennander (1906) advanced the hypothesis that all the internal organs which are innervated solely through the sympathetic nerves and the vagi, distal to the origin of the recurrent laryngeal nerves, are devoid of pain. This point of view obviously is untenable. Adequate physiological stimuli, *e. g.*, hunger contractions of the stomach, give rise to afferent impulses which result in sensations which in general are referable to the stomach. Adequate stimulation of various other viscera likewise gives rise to sensations referable to the organs in question.

The production of sensations is conditioned by the character of the stimulus and the tissue on which it acts. The absence of sensations due to manipulation, pinching, cutting or tearing of the visceral organs has been abundantly observed during operative procedures. In the application of any mechanical stimulus it may be observed that on passing from the skin into any of the orifices, *e. g.*, the mouth, there is a gradual diminution in sensitiveness as the area stimulated becomes farther removed from the external surface. Passing from the mouth distalward along the digestive tube, sensitivity is lost at some level of the esophagus. Passing from the perianal skin into the rectum, mechanical stimulation elicits no sensory response beyond the line which separates the skin from the mucous membrane. In investigations bearing on the problem of visceral pain it has almost invariably been found that when pain was produced by mechanical stimulation the stimulus affected tissues which are supplied by sensory cerebrospinal

no impulses which arise in this membrane reach the threshold of consciousness (Hoffmann 1920, Müller, 1921, Sunenauer, 1927, Capps, 1932)

Circulatory Organs — The Heart — The normal activities of the heart give rise to no sensations, although in many instances the impact of the apex against the thoracic wall may be distinctly perceived by the palpating hand It may be assumed that the portion of the thoracic wall in question has become so accustomed to the normal impact of the heart that it no longer gives rise to impulses which reach the threshold of consciousness Whenever the action of the heart becomes exaggerated as by physical exercise or emotional excitation, the beating of the heart becomes clearly perceptible In some instances the sensations are referable to the thoracic wall in others they appear to be referable to the heart The latter condition obtains particularly in cases of paroxysmal tachycardia in which patients not uncommonly interpret their sensations as due to the contraction of the heart musculature Not infrequently such patients also experience a feeling of inadequate heart action and 'heart flutter' Sensations due to exaggerated heart action which are clearly referable to the thoracic wall probably result from impulses arising in the thoracic wall due to the unusual impact of the apex beat Not infrequently, particularly in chronic cardiac conditions exaggerated or irregular heart action gives rise to no sensations Many patients with chronic cardiac disease are quite unable to form accurate judgments regarding their own cardiac activity

Injuries to the heart and inflammation of the cardiac muscle probably give rise to no sensations which are referable to the heart itself Stretching of the ventricular walls or the aortic ring likewise gives rise to no pain reaction (Sutton 1931) The endocardium also is insensitive to stimulation Inflammation or even ulceration of the endocardium gives rise to no sensations Frequent failures to recognize even ulcerative forms of endocarditis attest to the fact that such conditions may exist without giving rise to symptoms directly referable to the heart On the other hand endocarditis sometimes gives rise to discomfort such as a feeling of pressure in the cardiac region palpitation of the heart and dyspnea These sensations are not due to impulses arising in the endocardium but to impulses arising as a result of impaired circulation

Regarding the visceral pericardium it may be stated that the data available do not indicate that impulses arising in this tissue ever reach the threshold of consciousness According to Sutton (1931), pricking or pinching of the parietal pericardium elicits pain, but stretching or pulling it does not Pericarditis may exist in the absence of symptoms referable to the heart In severe cases of pericarditis, disturbances occur which give rise to sensations of pressure in the cardiac region and not infrequently to shortness of breath and a feeling of anxiety These sensations are not the result of impulses arising at the seat of the inflammatory process, but are manifestations of impaired heart action or pressure phenomena According to Capps (1932) pain associated with pericarditis is due mainly to three complications (1) Effusion exerting extreme tension on the pericardial sac which gives rise to a dull ache or feeling of oppression over the heart, (2) myocardial involvement due to embarrassment of the coronary circulation which gives rise to anginal pain, (3) pleuropericarditis the pain of which may be localized over the heart or referred to the neck or abdomen The pain associated with pneumonic and rheumatic pericarditis, according

to Capps, is due to pleuropericarditis which is a frequent complication in these infections. According to observations reported by Simenauer (1927), direct stimulation of the pericardium by contact at the apex of the heart resulted in a feeling of pressure on the inner side of the left arm. Moderate pressure on the pericardium of the right ventricle was not felt but heavier pressure resulted in an unpleasant feeling along the fourth rib. In experiments reported by Capps (1932), paracentesis of the pericardium at the level of the fifth or sixth interspace lateral to the mammary line elicited pain in the neck at a point along the trapezius ridge.

Limitation of the blood supply to the cardiac muscle, such as may be brought about by arteriosclerosis or spasm of the coronary arteries, not infrequently is accompanied by pain which is directly referable to the heart and pain which is referred to the thoracic wall and along the medial aspect of one or both arms. The intensity of these pains is comparable to that of pains caused by direct stimulation of the cerebrospinal nerves. They also are accompanied by a feeling of anxiety, vasoconstriction of the peripheral arteries, particularly in the face, and outbreaks of perspiration. The ischemic condition of the contracting cardiac muscle probably is a major factor in the production of the afferent impulses which give rise to these sensations. They are conducted centralward through visceral afferent fibers which traverse the sympathetic cardiac nerves, but the irradiation in the thoracic wall and upper extremities also involves somatic components of the spinal nerves through which the preganglionic and visceral afferent fibers involved in the innervation of the heart join the sympathetic trunks.

Pain caused by reduction of the blood supply to the myocardium has been amply demonstrated experimentally (Sutton and Leuth, 1930). Temporary partial or complete closure of either coronary artery or vein or both invariably gives rise to pain the severity of which varies with the degree of closure of the vessels (Sutton, 1931). When a single branch of a coronary artery is constricted the severity of the pain elicited also varies with the size of the vessel in question. Sutton and his collaborators could elicit cardiac pain responses in dogs and monkeys only by diminishing or stopping the flow of blood to the myocardium; consequently, they concluded that cardiac pain is caused either by ischemia or anoxemia of the cardiac muscle. Lambert (1931), on the other hand, advanced certain data in support of the theory that abnormal distention of the adventitia of the coronary arteries may give rise to cardiac pain.

In the dog, according to Sutton (1931), the afferent impulses resulting in cardiac pain reach the spinal cord mainly through the cardiac nerves on the left side The afferent fibers in question probably are mainly components of the upper two or three thoracic nerves (Mixter and White, 1931; Moore, 1938). Although pain of cardiac origin not uncommonly is referred to somatic tissues, Hashimoto (1930) demonstrated experimentally that stimulation of the afferent fibers which traverse the stellate ganglion elicits pain after section of the nerves involved in the brachial plexus. This result strongly suggests that cardiac pain may exist following section of all the somatic nerves involved in referred pains of cardiac origin.

The Blood Vessels.—Pain of vascular origin is a recognized clinical phenomenon but the blood vessels vary in sensitivity within relatively wide limits. The adequate stimuli for pain referable to the blood vessels are not fully known. Strong peripheral vasoconstriction not infrequently

is accompanied by pain. Evidence is not wanting which seems to support the theory that the pain is caused by the contraction of the vascular musculature. Other evidence seems to indicate that the ischemia produced in the tissues by the contraction of the blood vessels may be a contributing factor in the causation of pain. Under experimental conditions, pain may be produced by the injection of irritating substances into the arteries without spasm or stretching of the arterial muscle and without ischemia. The irritating substances apparently stimulate the afferent nerve endings which are located in proximity to the smaller arterial branches (Moore and Moore, 1933). To what extent chemical stimulation may play a part in the causation of pain in blood vessels under natural conditions as yet is unknown. Experimental and clinical data are not wanting which seem to support the assumption that accumulated metabolites in ischemic tissues may stimulate the receptors closely associated with the smaller blood vessels.

In experiments reported by Frohlich and Meyer (1932) the contraction of the vascular musculature elicited by the intravenous injection of adrenin produced no pain reaction, whereas the intra-arterial injection of barium chloride gave rise to intense pain. Distention of arteries, regardless of their caliber, according to Odermatt (1922), may give rise to pain due to the effect of distention on the periarterial nerve plexus. He also pointed out that ligation of certain arteries, *e.g.*, the common carotid, iliac and certain of the mesenteric arteries, commonly gives rise to pain, whereas ligation of certain other arteries, *e.g.*, the inferior thyroid, and veins rarely causes pain. These findings strongly suggest that the pain caused by ligation, like that caused by distention of arteries, is due to stimulation of the periarterial nerves. The findings of Spiegel and Wasserman (1926) that distention of a portion of the aorta, isolated by a ligature at either end, by introducing a physiologic saline solution under pressure, or the application of a stimulating substance to its outer surface gives rise to pain, support this point of view.

The intima of the larger vessels, according to Odermatt (1922), is insensitive to irritating substances. In his experiments pain reactions following the slow injection of such substances into a larger artery were initiated only after a latent period. When the artery was ligated distal to the point of injection so that the irritating substance could not flow into the capillary bed, no pain reactions occurred. On the basis of these findings, he concluded that the pain receptors stimulated by the irritating substance are not located in the larger vessels but are associated with the capillaries.

In experiments reported by Burget and Livingston (1931), the injection of a 5 per cent solution of lactic acid into the brachial artery of the dog elicited pain reactions similar to those elicited by the intra-arterial injection of barium chloride. In experiments on cats reported by Moore and Moore (1932), pain reactions were elicited by the injection of a concentrated solution of sodium iodide into the femoral artery. When the injected solution was confined to the arterial trunk by ligation of its branches no pain reaction occurred. When the femoral arterioles were blocked with lycopodium spores, the pain reaction was delayed. This delay suggested that the receptors stimulated by the injected solution are not located in the

arterial wall but either in relation to the arterioles or capillaries or in the adjacent tissues.

In a further study of the chemical stimulation of pain receptors, Moore, Moore and Singleton (1934) found that an isotonic or normal sodium chloride solution (0.9 per cent) may be injected intra-arterially in any quantity or at any rate without causing painful stimulation even though the artery may be visibly distended. If the sodium chloride concentration is gradually increased, pain is elicited when it reaches 3.0 per cent or half-molar strength. Other salt solutions produced similar results, *i. e.*, pain reactions were elicited when the total salt concentration of the injected solution approximated half-molar strength.

When sodium chloride solutions of progressively diminishing concentration were injected intra-arterially painful stimulation occurred when the salt content had fallen to 0.3 per cent or one-third isotonic. Other markedly hypotonic solutions and distilled water likewise elicited pain reactions. Normal or isotonic salt solutions also became irritating when they were rendered acid or alkaline. On the acid side, the solutions became irritating when the acidity reached a pH of 6.3; on the basic side, when the alkalinity reached a pH of 9.3. The pain receptors obviously are more sensitive to acid than to base.

Isotonic solutions of certain salts, although neutral in reaction, are irritating due to the nature of the metallic ions. For example, potassium chloride stimulates pain receptors in twentieth-molar, and barium chloride in fiftieth-molar concentration, as determined by the above investigators.

According to Bazett and McGlone (1928), the pain produced by arterial puncture can readily be differentiated from pain due to other causes. According to their findings, a dull aching sensation is felt when the needle reaches the arterial wall, which is less acute than the pain caused by simple puncture of the dermis but much less bearable. It is diffuse, often referred to a more distal position and not infrequently accompanied by uncontrollable reflex reactions. The subject may experience a sudden sensation of warmth, sweat profusely and then feel cold, faint or actually lose consciousness. The pain accompanying puncture of different arteries is not of equal intensity. For example, that produced by puncture of the brachial artery is less intense than that produced by puncture of the radial artery. Puncture of small arteries beneath the deep fascia, in the experiments of Bazett and McGlone, usually were accompanied by a dull aching pain which was not easily bearable and by reflex reactions of the fainting type. In general, puncture of the smaller arteries, except those in the dermis, was accompanied by more intense pain and more profound reflex reactions than puncture of the larger ones.

The sensations accompanying venipuncture, according to Bazett and McGlone, are similar to those caused by dermal puncture alone unless, as occasionally happens, a small nerve is affected. In the latter event, the sensations experienced are similar to those of arterial puncture but less severe.

Moore and Moore (1933) advanced experimental data which seem to indicate that the pain resulting from manipulation of the arteries is due to trauma of the accompanying nerves. They advanced the opinion that much of the pain which attends surgical procedures is caused by trauma to nerve fibers rather than by stimulation of sensory receptors and that

arterial distention and arterial spasm are only of secondary importance in the causation of pain. In cases in which vascular spasm is accompanied by pain, according to this view, there is present a secondary factor which probably is the real cause of the painful stimulation.

A sympathetic nervous factor in pain in the extremities associated with vasoconstriction induced by cold appears to be demonstrated by certain data reported by Hyndman and Wolkin (1942). In experiments carried out on patients who had undergone unilateral cervicothoracic or lumbar sympathectomy, these investigators found that when the nude subjects were exposed in the refrigerator the normally innervated hand or foot shortly began to sting and ache and felt decidedly cold subjectively, whereas these sensations were absent in the sympathectomized hand or foot even though the sympathectomized extremity was objectively as cold as the normally innervated one. When small blocks of ice were held in both hands the normally innervated one presently became painful whereas the sympathectomized one did not. Certain of their subjects were compelled because of pain to drop the ice from the normally innervated hand in fifteen to thirty seconds but retained it in the sympathectomized hand for several minutes without discomfort. While these data indicate that the sympathetic nerves play a role in pain associated with vasoconstriction, they do not indicate the mode of stimulation of the pain receptors.

The anatomical relationships of the fibers through which afferent impulses are conducted from the peripheral blood vessels to the central nervous system are not fully known but they are components of the dorsal spinal nerve roots. Some of these fibers traverse the sympathetic trunk (Kuntz and Farnsworth, 1931) but most of them do not. In experiments reported by Burget and Livingston (1931) removal of the stellate and second thoracic sympathetic ganglia did not alter the responses of the animal to the injection of lactic acid into the brachial artery on the same side. According to their findings afferent impulses from the brachial artery reach the spinal cord mainly through the dorsal roots of the seventh and eighth cervical and first thoracic nerves. Moore and Moore (1932) also reported that neither unilateral nor bilateral extirpation of the lumbar sympathetic trunk modified the pain reaction elicited by the injection of sodium iodide into the femoral artery. Obviously, most of the fibers involved in the conduction of afferent impulses from the peripheral arteries reach the spinal cord without traversing the sympathetic trunk. Moore and Singleton (1933) reported experimental data which indicate that the afferent nerve fibers which are stimulated by irritants injected into the hepatic, splenic and inferior mesenteric arteries enter the spinal cord in the thoracic region whereas the fibers of similar function related to the renal artery enter the spinal cord in the lumbar region. Afferent impulses which are conducted into the spinal cord from the blood vessels, according to Brjussowa and Lebedenko (1929), are conducted upward in the ventral portion of the lateral funiculus on both sides.

Alimentary Canal.—Esophagus.—The esophageal mucosa is sensitive in some degree, particularly to thermal stimulation. The presence of food in the esophagus usually is not perceived unless it causes marked distention of the esophageal musculature. In tests carried out on himself, Herz (1911) could discover no sensitivity of the mucous membrane of the esophagus to tactile stimulation, although the pharyngeal mucosa was found to be

sensitive. In the experiments of Payne and Poulton (1927), carried out on themselves, pain localized in the portion of the esophagus involved was produced by stretching of the esophageal wall. This pain was relieved by peristaltic contractions which overcame the stretch, or by postural adaptation of the viscus which increased its capacity. Peristaltic contractions which failed to overcome the stretch resulted in more intense pain. Continuous stretching of the esophagus gave rise to burning pain (heartburn). They also experienced pain in the esophagus during muscular relaxation following a peristaltic wave. In their experiments, pain in the esophagus always was associated with high tonus and probably was caused by stretching and deformation of sensory nerve endings in the esophageal wall. In experiments reported by Polland and Bloomfield (1931), inflation of small balloons in the esophagus gave rise to sensations akin to pain which usually could not be accurately described by the subject and frequently were identical with spontaneous "digestive" discomforts. These sensations were localized most frequently at the xyphoid or in the suprasternal notch, sometimes over the anterior chest wall or in the back and rarely in the neck or face.

In experiments reported by Jones (1938), in which the esophagus was distended or blocked at different levels by means of an inflated balloon, most of the subjects felt only a sensation of uncomfortable fullness when the balloon was inflated in the upper portion, and less than 20 per cent noted a burning sensation. As the stimulus was applied at lower levels the sensation of fullness, or pressure, diminished and that of heartburn increased. When the balloon was inflated in the lower portion of the esophagus most of the subjects experienced definite "heartburn." This sensation probably is associated with reversed peristaltic contractions of the esophageal musculature. Fluoroscopic examination of patients experiencing heartburn, as reported by Jones, showed definite reversed peristaltic activity in the lower portion of the esophagus. When this activity subsided the sensation of heartburn almost completely disappeared, only to reappear with increased intensity when the antiperistaltic contractions recurred. In most instances the sensations were localized near the midsternal line and approximately at the level of the stimulus.

Stomach.—Many of the recorded observations regarding the sensitivity of the stomach support the theory that this viscus is insensitive to mechanical, chemical, thermal and electrical stimuli. It may be cut, torn or otherwise injured during operative procedures, carried out under local anesthesia of the abdominal wall, without giving rise to pain. Certain forms of [illegible] stimulation give rise to painful sensations. For example, strong chemical stimulation of the gastric mucosa always gives rise to pain. [illegible] types of gastritis, substances normal for the stomach [illegible] or gastric juice, may cause pain. Strong tonic contractions [illegible] also give rise to pain. Such reactions also may be a [illegible] resulting from the destructive action of chemical substances on [illegible] of the normal stomach or normal stimulation of the hyper[illegible] Herz (1911) advanced the theory that all so-called gastric pain [illegible] strong contraction of the pylorus and the pyloric portion of the stomach. According to Carlson (1916), gastric [illegible] probably is [illegible] but the injured mucosa must be r[illegible] distention of the stomach causes pain [illegible]

but there is no evidence that the nerves supplying the mucosa play any part in such pain. According to Carlson the only pains arising from the stomach under normal physiologic conditions are the pangs of hunger, in which the innervation of the mucosa plays no part. All pains due to impulses arising in the gastric mucosa probably should be regarded as indications of pathologic processes, i. e., either normal stimuli acting on the hypersensitive mucosa or destructive stimuli acting on the normal mucosa.

The absence of tactile sensibility in the normal gastric mucosa is quite generally conceded. Its sensitivity to thermal stimulation has been studied extensively. Most of the recorded observations indicate that hot or cold substances introduced into the stomach give rise to vague sensations of heat or cold in the region of the epigastrium but not all the investigators agree that the sensations arise in the gastric mucosa. For example, Weber (1846) assumed that sufficient conduction takes place through the walls of the stomach and abdomen to stimulate the temperature receptors in the skin. Mackenzie explained the temperature sensations resulting from the introduction of hot and cold water into the stomach on the basis of reflex vasomotor changes in the skin of the abdomen.

In experiments carried out on themselves, Neumann (1906) and Roux (1907) experienced temperature sensations in the stomach when hot or cold water was introduced into it through a double rubber tube. Boring (1915) reported experiments in which water at 30° C. produced a sensation of cold and water at 40° C. a sensation of warmth in the stomach. He advanced the opinion that these sensations arise either in the stomach or in some tissue nearer to it than the esophagus or the abdominal wall. On the basis of the results of an extensive series of experiments carried out on himself and other persons Carlson (1916) concluded that the mucosa of the stomach like that of the esophagus is supplied with receptors for heat and cold but these receptors either are less abundant or their threshold of stimulation is higher in the stomach than in the esophagus.

Regarding the sensitivity of the gastric mucosa to chemical stimulation it may be stated that substances like pepper, mustard, strong alcohol, acid (5 to 20 per cent HCl), etc., introduced into the stomach through a tube in sufficient quantity give rise to varying degrees of pain accompanied at first by a sensation of warmth in the stomach (Carlson, 1916). All chemicals taken into the stomach in sufficient concentration to cause pain probably injure the mucosa and the nerve endings in it, as is indicated by the development of gastritis. When chemical substances are taken into the stomach in dilutions which do not cause pain or discomfort, their contact with the mucosa may still give rise to sensations which are not akin to pain but related to appetite. In Carlson's experiments, the sensations produced by beer, wine, weak acid (0.5 to 2 per cent HCl), weak alcohol or carbonated drinks introduced into the stomach through a tube, were rather transitory, but characteristic, and could not always be distinguished from appetite. The fact that these sensations arise immediately when the appropriate substances are introduced into the stomach, even though this organ is quiescent and very greatly relaxed, indicates that they are due to stimulation of receptors in the gastric mucosa and do not depend on gastric motility. They also differ qualitatively from the sensation of relief following relaxation of the stomach at the end of a period of hunger

contractions in that they possess the positive character that directs attention to food and eating When the gastric mucosa is stimulated in this manner during a period of hunger contractions it is quite impossible to differentiate the sensation caused by the chemical stimulus from the sensation of relief from hunger It is evident, therefore, that chemical stimulation of the gastric mucosa plays an important rôle in appetite and the desire for food

On the basis of extensive experimental observations and a review of the literature bearing on the subject, Herz (1911) concluded that "the sensation of fullness in the stomach is due to tension on its muscular coat, and depends very little, and only in extreme cases, on the stretching of the abdominal wall" Impulses arising in the gastric mucosa probably play no part in the sensations of fullness As pointed out by Carlson (1916), tension on the gastric musculature alone, *i e.*, intragastric pressure, does not result in a sensation of fullness under all conditions The intragastric pressure at the height of a period of hunger contractions of the empty stomach, when distended by a rubber balloon, frequently exceeds that which, according to Herz, is required to cause a sensation of fullness, yet the sensation experienced under these conditions is not one of fullness but of emptiness Carlson, therefore, concluded "that a certain amount of tonus reaction of the stomach must be present before tension or pressure on the walls of the stomach produce the sensation of fullness"

The sensation of satiety following a palatable meal probably arises independently of impulses emanating from the gastric mucosa. In order to insure this sensation, eating must be preceded by some degree of hunger and appetite, the food must be palatable and must be eaten in sufficient quantity to produce moderate distention of the stomach but not the sensation of fullness The sensation of satiety, according to Carlson, "involves the element of contrast between the uncomfortable tension of hunger and the sensation of fulness, together with the lingering memories of the taste and smell of the food"

Nausea is a very complex sensation which is referable only in part to the stomach It may be initiated by stimulation of the gastric mucosa, but usually involves other factors, and not infrequently arises entirely independently of gastric disorder It probably always involves a characteristic feeling of distress referable to the stomach Under certain conditions, nausea seems to be allied to hunger. In Boring's experiments, some of the subjects (normal men) confused mild nausea with hunger. Such confusion is regarded by Carlson either as pathologic or due to superficial analysis. Both nausea and hunger involve sensations of uncomfortable tension and pain and cause salivation In some persons, both these states also involve bodily weakness, headache, dizziness, etc., but "the distinct 'sickness' character of the gastric distress in nausea," according to Carlson, is lacking in normal persons in any stage of hunger. The central effects of nausea, in normal persons also are unlike those produced by hunger Nausea is incompatible with appetite; hunger commonly intensifies the desire for food Since hunger, though normally caused by stimulation of the kinesthetic nerves of the stomach, like nausea, may be caused by stimulation of the nerves of the gastric mucosa, it is not unlikely that intense hunger, in persons with an unstable central nervous organization, may be accompanied by nausea or become apparently identical with it

The gastric factor in appetite depends mainly on moderate chemical stimulation of the nerves of the gastric mucosa, while the sensation of hunger arises from stimulation of nerves in the submucosa or muscularis by a certain type of contraction of the empty or nearly empty stomach which has been called the hunger contraction (Carlson 1916) Although certain investigators had previously pointed out that the stomachs in starving men and animals are tonically contracted, Boldireff (1905) carried out the first systematic study of gastric motility during starvation He observed in dogs, at least during the first three to four days of starvation, that the stomach exhibits alternate periods of strong contractions and absolute quiescence In his experiments the periods of contraction lasted 20 to 30 minutes, the periods of quiescence 1 5 to 2 5 hours During a period of activity 10 to 20 contractions separated by intervals of 1 to 1 5 minutes took place The contractions were at first feeble and gradually reached their maximum strength at the end of the period Contractions of the intestine also were observed during these periods Boldireff observed that these contractions of the empty stomach are stronger than gastric peristalsis during digestion He did not associate them with the cause of the sensation of hunger mainly because he observed that they diminish in strength with the length of the period of starvation He advanced the opinion that the contractions of the stomach and intestine during starvation are initiated through the vagi by the state of hunger in the brain

In a series of experiments carried out on a man in which a graphic record of the gastric contractions was obtained by means of a rubber balloon which had been swallowed into the stomach Cannon and Washburn (1911) showed that the periods of contractions of the empty stomach coincide with the periods of hunger sensations and that each contraction synchronizes with a hunger pang They also obtained evidence that contractions occur in the lower third of the esophagus which are synchronous with the gastric contractions They concluded that esophageal contractions play a part in hunger They also noted that the sensation of hunger tends to lag behind the gastric contraction both at its beginning and its termination On the basis of their experimental results, they concluded that these contractions of the stomach and lower third of the esophagus cause the sensation of hunger through stimulation of sensory nerves

Although the assumption of Cannon and Washburn was essentially correct it remained for Carlson and his students (1912) to demonstrate, in man and experimental animals that the sensation of hunger is caused by contractions of the empty or nearly empty stomach of a certain type and that the sensory nerve fibers involved are not those which supply the gastric mucosa but those which supply the submucosa or the muscularis Carlson (1914) also obtained certain experimental evidence which he interpreted as indicating that the hunger contractions are initiated in the stomach itself and, in a large measure, are independent of efferent impulses emanating from the central nervous system In his experiments, moderate exercise had little stimulating effect on gastric tonus and hunger contractions Moderate stimulation of the nerve endings for cold had no effect but intense stimulation of these nerve endings inhibited hunger contractions As an after-effect there was an increase in gastric tonus and hunger contractions Intellectual processes seemed to have no effect except as

they caused inhibition of gastric tonus and hunger contractions through the splanchnic nerves. On the basis of these experimental findings, he concluded that "in normal individuals (man, dog) the vagogastric tonus apparatus, at least so far as it concerns the empty stomach, is physiologically isolated from the exteroceptors and from many, if not all, central processes." He admitted however, that this mechanism is affected by the nutrient content of the blood when he advanced the opinion that "the biological significance of this exceptional and unique isolation of the tonus apparatus of the hunger mechanism probably lies in the importance of the hunger mechanism being regulated on its positive side primarily by the state of nutrition, that is, through the blood rather than by the fleeting changes in the nervous system."

Depletion of the nutrient substances in the circulating blood is an important factor in the production of hunger. Emptiness of the stomach alone is not sufficient to cause hunger The stomach may be empty for several hours before the sensation of hunger arises The sensation of hunger, furthermore, subsides temporarily following the subcutaneous injection of a nutrient solution, *e g.*, glucose, even though the stomach remains empty (Thoma, 1915). It also has been observed clinically that the stomach, under certain pathologic conditions, may remain empty for days without giving rise to hunger sensations. On the other hand, a patient with pyloric stenosis may experience intense hunger, although the stomach is filled with food.

Moderate physical exercise, as pointed out by Carlson, has little immediate effect on the hunger contractions of the stomach. Vigorous physical exercise hastens the onset of hunger. This points very definitely to the nutritive content of the blood as a factor in the sensation of hunger. Thoma (1915) advanced the opinion that a certain center in the brain reacts to the lack of nutrient material in the blood by sending out efferent impulses which bring about reactions, which in turn initiate afferent impulses resulting in the sensation of hunger, just as the respiratory center reacts to the lack of oxygen in the blood by sending out efferent impulses which accelerate the respiratory movements. He also advanced the opinion that the center in question is closely associated with the temperature-regulating center, as is indicated by the fact that hunger not uncommonly subsides during fever. He further observed that animals in which the so-called temperature puncture in the diencephalon was successfully carried out lost their desire for food Although unable to localize the center in question more definitely, he assumed that an aggregate of nerve cells exists in the brain stem which reacts to the lack of nutrient material in the blood by giving rise to efferent impulses and that these impulses are conducted peripheralward through the vagus nerves and call forth contractions of the empty stomach as well as secretory activity of the gastric glands. The contractions of the stomach in turn generate afferent impulses which result in sensations referable to that organ.

Although the stomach may be cut, torn, or otherwise injured without giving rise to pain, impulses arising in it, under certain pathologic conditions, give rise to painful sensations which are directly referable to this organ The same impulses may also give rise to sensations which are referable to the body wall.

The chief causes of gastric pain undoubtedly are hyperdistention of the

stomach wall and spastic contractions of the gastric musculature (Smith and Paul, 1931). Bloomfield and Polland (1931) reported the results of experiments in which inflation of a balloon in the stomach gave rise to sensations which usually were described by the subjects as feelings of fullness, tightness or pressure with a superadded element of pain. These sensations could not be accurately localized but in most instances they could be recognized as arising within the abdomen near the medial plane. In experiments reported by Boyden and Rigler (1931) faradic stimulation of the gastric mucosa by means of a Rehfuss tube the metal end of which had been converted into an electrode and swallowed to the desired depth caused a ring of contraction of the gastric musculature accompanied by sensations ranging from barely perceptible feelings of pressure to severe colicy pains localized deep in the body wall in the upper abdominal quadrants. In experiments on dogs Balchum and Weaver (1943) elicited pain reactions by inflating the stomach with an air-filled balloon until the intragastric pressure was elevated to 50 to 60 mm. of mercury. The threshold for painful stimulation was fairly constant in every individual animal and did not change significantly after repeated inflations of the stomach over periods as long as seven months. The impulses of pain were conducted centralward only through afferent components of the splanchnic nerves and did not give rise to recognizable referred phenomena. Infiltration of the skin over the back and abdomen with procaine or bilateral section of the lower seven intercostal nerves and the anterior roots of the thoracic and lumbar spinal nerves neither abolished the pain elicited by inflation of the stomach nor appreciably elevated the threshold of painful stimulation.

Gastric ulcer involving only the gastric mucosa may be the underlying cause of gastric pain but gastric ulceration may go on to the point of perforation in some cases without giving rise to pain. It seems highly improbable that the pain which in many cases is associated with gastric ulcer is mediated through the nerves supplying the gastric mucosa. Not uncommonly the onset of this pain bears a definite relationship to the time of eating. It does not occur immediately following the ingestion of food but after the food has become thoroughly mixed with gastric juice and is ready to be discharged into the duodenum. As has been shown by fluoroscopic examination of patients with gastric ulcer, the pain in many instances coincides with a period of peristaltic contractions which sweep over the pyloric portion of the stomach against the contracted pylorus. These contractions of the pars pylorica probably constitute the major factor in the genesis of gastric pain under these conditions. According to Carlson (1918) they usually are no stronger than the normal peristaltic contractions of the filled stomach or the hunger contractions of the empty stomach. A condition of hyperexcitability of the gastric pain nerves therefore is indicated in ulcer patients who experience the typical ulcer pains.

Certain patients with gastric ulcer also experience pain while the stomach is empty. It has been assumed by certain investigators that the contractions which give rise to the pain in such cases are caused by gastric hyperacidity. As pointed out by Carlson, the motility of the stomach is in a large measure independent of the chemical reaction of the gastric contents. High gastric acidity, however, intensifies and prolongs the duodenal reflex

contractions of the pylorus and induces strong duodenal contractions. These pains commonly are alleviated by the ingestion of substances (protein food water, alkalies) which temporarily lower gastric acidity, provided there is sufficient relaxation of the pylorus to permit the gastric contents to pass into the duodenum. Ulcer pains which are due to tonus or contractions of the body of the stomach commonly are alleviated temporarily by any measure which inhibits or decreases gastric tonus, irrespective of the chemical reaction of the stomach contents. The continuous pain in the epigastric region, which is present in certain cases of gastric ulcer, probably is due to persistent exaggerated tonus of the stomach or pylorus. The more severe exacerbations of this pain probably are due to pyloric spasm (Carlson, 1918).

Palmer (1927) was able to elicit pain, in cases of gastric ulcer, when the acidity of the stomach contents was normal. In general, he found little connection between the pain and gastric tonus or motility, although he conceded that gastric hyperperistalsis may be a contributing factor in some cases. Strauss (1928), who had previously maintained that free hydrochloric acid in the stomach and a zone of inflammation around the eroded area are important factors in the production of ulcer pains, was convinced by the results of his later studies that an excessive amount of normal gastric juice may stimulate the nerves through which the pain of gastric ulcer is mediated. He also conceded that gastric peristalsis may play a contributing rôle. According to Palmer and Heinz (1934), the pain of gastric or duodenal ulcer has its origin at the site of the lesion. The usual stimulus is free hydrochloric acid acting upon an irritable mechanism located within the lesion or adjacent to it. This mechanism also may be stimulated by peristaltic contractions or local spasm.

On the basis of extensive clinical and experimental studies, Balint (1928) advanced the conclusion that the pain of gastric ulcer is not caused by gastric hyperacidity but by two factors acting simultaneously, viz.: contraction of the gastric musculature and a shift in the hydrogen-ion concentration of the blood toward the acid side. He called attention to the fact, recorded by various investigators, that the introduction of acid in relatively high concentration into the stomach of a gastric ulcer patient does not elicit pain. In his own clinical experiments, the gastric ulcer pains subsided following the contemplation and mastication of palatable food by the patient, although none of it was swallowed. The effect on the ulcer pain of such sham feeding was similar to that of the introduction of food into the stomach, although the acidity of the gastric contents was appreciably increased by reason of the increased activity of the gastric glands due to the stimulus afforded by the sham feeding. Balint also maintained that the alleviation of ulcer pain by alkali therapy does not depend on neutralization of the acid in the stomach, since such therapy not infrequently results in the alleviation of ulcer pains in cases which exhibit anacidity as well as in cases which still exhibit gastric hyperacidity following alkali treatment. He also pointed out that the intravenous injection of alkali produces the same result. This supports the conclusion that the therapeutic effect of alkali, in cases of gastric ulcer, depends mainly on its effect on the hydrogen-ion concentration of the blood. This conclusion also is supported by the fact that ulcer pains are alleviated by hyperventilation of the lungs, which has the same effect on the acid-base balance of the blood

as alkali therapy. That changes in the acid base balance of the blood toward the acid side play a rôle in the causation of ulcer pains also is suggested by the fact that other therapeutic agents which tend to shift the acid base balance toward the basic side, e. g., atropine, roentgen radiation, etc., also tend to alleviate these pains whereas measures which tend to shift the acid base balance of the blood toward the acid side, e. g., physical exertion, aggravate the ulcer pains. Inasmuch as gastric ulcer pains commonly accompany gastric motility which must be regarded as a factor in their causation, it may be assumed that the influence of changes in the acid base reaction of the blood in the causation of ulcer pains is due at least in part to the effect of these changes on the functional balance between the sympathetic and parasympathetic components of the autonomic system which in turn is reflected in the gastric motility.

The pain experienced in cases of acute gastritis also is due to impulses arising in the deeper layers of the stomach wall. It arises only when the stomach becomes distended by reason of faulty emptying or generation of gas and probably is due to hyperdistention of the stomach wall or contraction of the gastric musculature. The normal stomach may react in essentially the same manner when overfilled with food of low digestibility. Under these conditions the subject may experience discomfort due to pressure or even acute pain.

Intestine.—Like the stomach the intestine is insensitive to the ordinary stimuli. Appropriate stimulation of the intestine gives rise to impulses which result in pain of varying degrees of intensity. In the experiments of Bloomfield and Polland (1931) moderate inflation of a small balloon in various parts of the small and large intestine gave rise to sensations which the subject usually recognized as similar to spontaneous discomforts previously experienced and not unlike sensations of overeating, indigestion, urge to evacuation, etc. Not infrequently, strong contractions of the intestine give rise to pain which is more or less definitely localizable in the abdomen. Limitation of the blood supply to the intestine such as occurs in cases of advanced arteriosclerosis of the aorta constricting the portals of the mesenteric arteries also gives rise to intense intestinal pain particularly while digestive activity is at its height (Muller 1924). On the other hand ulceration of the intestine such as occurs in typhoid and tuberculosis may exist without giving rise to any sensations. Such lesions may bring about hypermotility of the intestine through stimulation of the enteric plexuses which under certain conditions results in pain. The powerful contractions of the intestinal musculature which occur in cases of partial or complete intestinal occlusion resulting from carcinoma or other causes, also give rise to pain of varying degrees of intensity.

In the experiments reported by Boyden and Rigler (1934) the results of faradic stimulation of the duodenal mucosa were comparable to those of stimulation of the gastric mucosa. The sphincteric contraction of the musculature initiated at the level of the stimulation was followed by increased peristalsis distal to that level. The accompanying sensations were localized in the upper abdominal quadrants. As the electrode was drawn upward through successive portions of the duodenum and stomach, the sites of the pain progressively indicated the positions of these organs but with marked aberrancy in many instances. The visceral nature of this pain is indicated by the observation of Boyden and Rigler that it persists

under an anesthetized cutaneous area. Pain caused by inflation of a balloon in the intestine, as reported by Jones (1938), is felt most commonly in the midline or near it. With the balloon in the proximal portion of the duodenum the usual site of the pain is in the epigastrium. As the more distal portion of the duodenum becomes distended, the pain or discomfort tends to descend into the low epigastric or upper umbilical areas. Pain or discomfort due to distention of any portion of the jejunum and ileum, except the lower ileum, is felt most commonly near the umbilical level. Distention of the terminal portion of the ileum frequently is felt in the umbilical area and sometimes at lower levels. Not infrequently the sensation is localized some distance from the midline. Pain caused by distention of the large intestine, in Jones' experiments, was less acute and less definitely localized than that arising in the small intestine. It was commonly felt below the umbilicus and there was no constant relationship between the actual position of the balloon and the point in the lower abdomen at which the sensation was localized. With some exceptions, the pain was felt near the midline or to the left. Pain caused by distention of the cecum just distal to the ileocecal valve was commonly localized at the usual site of appendiceal pain, i. e., in the region of McBurney's point.

The pain in duodenal ulcer has been ascribed to irritation of the exposed nerve endings in the ulcerated area by the acid gastric juice (Gonnin 1908; Palmer, 1927; and others), mechanical irritation by coarse particles of food (Pick, 1913), spasm of the pyloric sphincter or duodenal ca (Glaessner and Kreuzfuchs, 1913), tension due to inhibition of relax of the pyloric sphincter combined with strong gastric peristalsis (E 1921), and various other causes. Wilson (1928) found no direct rel ship between the acidity of the gastric contents and the occurrence in patients with duodenal ulcer, although the common experience from the pain of duodenal ulcer by the administration of alkalies suggests that gastric hyperacidity may be a factor in the prod pain. He also found no direct relationship between the occurrence in duodenal ulcer and gastric motility or the tonic state of th sphincter. In his experience, the pain of duodenal ulcer nearly relieved by squeezing gastric contents into the duodenal caput of the gastric acidity. In those cases in which the pain was by this procedure, it was apparent that the musculature of th caput was not relaxed. On the basis of his findings, he a hypothesis that the pain of duodenal ulcer is due to sustained of the duodenal caput.

Dragstedt and Palmer (1932) reported certain observatio patient with duodenal ulcer, operated upon under local anes have a direct bearing on the causes of pain referable to gastr ulcers. A chronic ulcer approximately 2 cm. in diameter the anterior wall of the first part of the duodenum. Gen serosa with the gloved finger over the ulcer caused the pati of pain similar to his ulcer distress. Massaging the reg gently but firmly caused severe distress. on pulling it toward the left, also gave rise to The injection of 20 cc. of a 5 per cent sol the lumen of the pylorus by means of a hy was present relieved it almost immedi

about five minutes The injection of 20 cc of a 0 5 per cent solution of hydrochloric acid into the duodenum in the same manner gave rise to a burning pain almost immediately which persisted until a solution of sodium bicarbonate was injected The relief obtained by this injection was less striking than that obtained by the first injection of sodium bicarbonate and did not persist A few minutes later, the patient complained of severe cramping pain, when a deep circular contraction ring was observed just distal to the ulcer As this contraction advanced distalward, it was succeeded by several similar waves of contraction, during which time the cramp-like pain continued It is interesting to note in this connection that peristaltic waves passing over the pyloric antrum were observed at times when no pain was experienced These observations show clearly that typical ulcer pain and distress may be caused by mechanical and chemical stimulation of the ulcer region as well as by marked contraction of the musculature in that region or immediately adjacent to it They also suggest the rationality of alkali therapy in cases of gastric and duodenal ulcers

The terminal portion of the large intestine viz, the pelvic colon and rectum, are sensitive in a certain degree to stimuli other than those which give rise to pain This is in keeping with the functional requirements of the lower portion of the digestive tube and illustrates the general principle that receptors for various types of stimuli exist in all parts of the body in which they are demanded by the vital interests of the organism

Liver and Biliary System — The parenchyma of the liver may be regarded as insensitive to the ordinary stimuli It may be cut torn or otherwise injured without giving rise to sensations Inflammatory processes and ulceration in the liver give rise to no impulses which reach the threshold of consciousness The serous covering of the liver also is insensitive Inflammatory processes which involve the parietal peritoneum give rise to painful sensations but they are not directly referable to the liver Rapid enlargement of the liver such as occurs in cases of cardiac decompensation, not infrequently gives rise to pain and sensations of pressure in the epigastric region probably due to distention of the hepatic capsule and the weight of the enlarged organ pulling downward on its attachment to the diaphragm

The pain experienced in attacks of biliary colic and other disturbances of the biliary system, like pain arising in other visceral organs containing smooth muscle probably is due to impulses arising from hyperdistention or spastic contraction of the musculature of the bile ducts In an experimental investigation carried out on dogs Gubergritz Itschenko and Goldstein (1926) elicited pain reactions by distending parts of the biliary system with warm water introduced into the common bile duct through a cannula inserted through its opening into the intestine On the basis of their experimental results, they concluded that both spasm and distention of the biliary musculature may give rise to pain A certain degree of distention seemed to be necessary to produce pain, and the pain became more intense as the distention was increased by introducing more water, but this was not the only factor involved Distention of the bile ducts with water seemed to cause spastic contraction of their smooth musculature which in turn increased the pain Distention of the bile ducts alone may give rise to slight pain but spastic contraction of the biliary musculature probably constitutes the major factor in the genesis of biliary pain These

experimental findings are in full accord with clinical observations. The dull pain associated with biliary stasis probably is due mainly to distention of the biliary musculature The acute pain of biliary colic is due to spastic contraction of this musculature. This pain commonly is localized in the region of the gall bladder. Not infrequently it cannot be clearly dissociated from the accompanying gastric pain. The true visceral nature of gall bladder pain is indicated by the observations that distention of the gall bladder in animals elicits pain reactions after desensitization of the appropriate area of the body wall by section of the intercostal nerves distal to the communicating rami (Davis, Pollock and Stone, 1932) and after complete section of the ventral portion of the lateral funiculus in the spinal cord and even bilateral hemisection of the cord at separate levels (Davis, Hart and Crain, 1929) The impulses resulting in pain of biliary origin are conducted into the spinal cord mainly via the splanchnic nerves on the right side

Pancreas.—The pancreas may be regarded as insensitive to the ordinary stimuli, yet certain pancreatic lesions are known to give rise to excruciating pain The clinical manifestations, in these cases, are so complex that it is quite impossible to determine the exact sources of the afferent impulses involved. There is no clear evidence that these impulses arise solely in the pancreas They probably arise in part in the blood vessels through which the pancreas is supplied. If, by reason of a pancreatic lesion, autodigestion takes place, this may involve not only the large abdominal sympathetic plexuses but also components of the spinal nerves.

Spleen.—The spleen may be regarded as insensitive to the ordinary stimuli. Impulses arising in this organ probably do not reach the threshold of consciousness. Inflammation of the serosa of the spleen may give rise to pain, probably due to involvement of the parietal peritoneum. The pain associated with enlargement of the spleen probably is due to traction of the splenic attachments.

Kidney.—The kidneys, like other visceral organs, may be cut, torn or otherwise injured without causing sensations The renal pelvis seems to be sensitive under certain conditions Although mere contact results in no sensations, contact of this part of the organ with hot or cold objects gives rise to pain (Gubergritz and Itschenko, 1926). In most cases of renal pain, the afferent impulses involved probably arise in the renal pelvis. Traction on the kidney also gives rise to pain, undoubtedly due to the pull on the renal blood vessels and the parietal peritoneum. Kappis expressed the opinion that renal pain can be explained most satisfactorily on the basis of stimulation of receptors in the prerenal peritoneum, particularly at the level of the root of the kidney. Renal pain commonly is localized in the back just below the costal margin and not uncommonly radiates to the ovary or testis and along the ureter to the bladder. In some cases, it also radiates into the thigh

Pathological conditions of the kidney commonly are accompanied by pain. In a limited number of cases, the pain is due at least in part to traction caused by shifting of the position of the organ. In cases of renal enlargement, the sensory nerves in the adjacent parietal peritoneum may be stimulated by pressure. This may be regarded as one of the major factors in renal pain Distention of the renal capsule also has been regarded as a factor in producing painful stimulation. A shrunken kidney also may give

rise to pain although its capsule is not under tension. In experiments reported by Gubergritz and Itschenko (1926) distention of the renal pelvis by the introduction of water through the ureteral catheter commonly elicited pain reactions except when the renal plexus had previously been divided. They regarded distention of the renal capsule only as a secondary factor in the production of renal pain. Inasmuch as pain reactions could not be elicited by distention of the renal pelvis following denervation of the kidney by section of the nerves along the renal vessels they concluded that the afferent impulses involved are conducted through the renal plexus and reach the spinal cord via the splanchnic nerves. Although pain of renal origin under certain conditions may involve conduction through somatic afferent fibers supplying the adjacent parietal peritoneum, it may in general be assumed that impulses which give rise to renal pain are mediated through the visceral afferent fibers which traverse the renal plexus.

Ureter.—Ureteral catheterization in experimental animals, according to Gubergritz and Itschenko (1926), does not necessarily give rise to pain. In clinical experiments reported by Okerblad and Carlson (1937) direct faradic stimulation of the ureter by means of a catheter electrode in the lumen elicited pain which in most instances was referred. With the electrode in the lower portion of the ureter the pain usually was felt in the suprapubic area near the midline and in some instances on the medial and lateral sides of the thigh and the medial side of the leg. Stimulation of the proximal portion of the ureter elicited pain particularly over the anterior portion of the iliac crest and the iliac spine. Since the position of the ureter is retroperitoneal, it seems not improbable that the stimulus employed in these experiments may have affected somatic receptors, thus facilitating the radiation of pain to the somatic areas indicated.

Urinary Bladder.—Sensitivity of the urinary bladder to certain types of stimulation is generally conceded. Under normal conditions the urge to micturate depends on afferent impulses which arise in the bladder; consequently sensations which have their origin in the urinary bladder play an important role in the functional regulation of this viscus. Overdistention of the bladder not only results in a strong desire to micturate but also gives rise to acute pain.

The mucosa of the bladder, like that of the gastro-intestinal canal, is insensitive to most of the ordinary stimuli, but parts of it are sensitive to tactile as well as painful stimulation (Learmonth, 1931). Irrigation of the bladder with hot or cold water gives rise to no temperature sensations. The pain caused by electrical stimulation of the bladder mucosa probably is due to contraction of the bladder musculature. The pain resulting from cystitis and ulceration of the bladder mucosa likewise probably is not due to the direct effect of the lesion of the mucosa alone but mainly to reflex muscle spasm.

Under normal conditions the urge to micturate arises only after some degree of distention of the bladder wall, but distention of the bladder musculature probably is not the cause of the sensation. If it were, the urge to micturate would be continuous and become progressively stronger as the bladder becomes more and more distended by the increasing volume of its contents, which is not the case. According to Schwartz (1920), the sensations which give rise to the urge to micturate have their cause in the contraction of the detrusor muscle. On the other hand, Adler (1920)

advanced the opinion that these sensations are caused by contractions of the internal sphincter vesicæ. Both these processes probably play a part in the production of vesical sensations. Müller (1924) expressed the opinion that the indefinite sensations felt in the region of the bladder, which are not definitely localizable, are caused by contraction of the bladder musculature, while the more acute sensations which are more or less definitely localizable at the neck of the bladder are caused by contraction of the musculature in that region.

Impulses arising in the bladder reach the spinal cord via both the hypogastric and pelvic nerves. Those which give rise to the ordinary vesical sensations are mediated mainly through the pelvic nerves. According to Fröhlich and Meyer (1922), the sensitivity of the bladder is not affected by section of the hypogastric nerves. On the other hand, Pieri (1926) reported incomplete relief of pain due to disease of the bladder following hypogastric nerve section. According to Learmonth (1932), section of the hypogastric nerves leaves the ordinary sensibility of the bladder unaltered but renders it definitely less sensitive to uncoördinated and spasmodic contractions: consequently, certain pains of vesical origin may be abolished by this operative procedure. Impulses arising in the sphincters of the bladder reach the central nervous system via the pudendal nerve.

Female Genitalia.—The vaginal mucosa, like the mucosa of the other hollow viscera, may be regarded as insensitive to the ordinary stimuli. These stimuli when applied to the uterus, Fallopian tubes or ovaries give rise to no sensations unless they cause traction on the parietal peritoneum of the attachments of the organs in question to the body wall. Pains arising in the uterus are due mainly to contractions of the uterine musculature. Pains resulting from displacement of the uterus are not directly referable to this organ. They probably are due mainly to the effect of its displacement on adjacent structures.

Sensory Conduction from Cephalic Areas via Spinal Nerve Components.—On the basis of experimental findings and clinical observations, certain investigators, particularly Foerster, Altenburger and Kroll (1929), have assumed that the nerves extending upward from the superior cervical ganglion, which represent the extension of the sympathetic trunk into the head, include afferent fibers which traverse the cervical sympathetic trunk and enter the spinal cord via the posterior roots of the upper thoracic nerves. Anatomical proof of the existence of such fibers is not forthcoming. Clinical observations following total and subtotal resection of the sensory root of the trigeminal nerve for the relief of trigeminal neuralgia led Fraser to suspect that fibers extending from the cervical sympathetic into the head play a rôle in certain sensory phenomena in the area of distribution of the trigeminal nerve, particularly following sensory trigeminal paralysis. The findings reported by Helson (1932), who carried out an intensive study of the different forms of sensibility detectible in the area of distribution of the trigeminal nerve following section of its sensory root in certain of Fraser's patients, tended to confirm this view. According to his findings, sensibility to light touch and ordinary painful stimuli is lost permanently, sensibility to deep pressure and the ability to localize touch are greatly reduced immediately after the operation but later are gradually restored to an appreciable degree, temperature stimuli between 15° and 45° C. evoke no sensations, but hot stimuli (60° to 75° C.) usually give

stinging or pricking sensations. In individuals who also had been subjected to cervical sympathectomy, so that the trigeminal area was deprived of its sympathetic innervation as well as the sensory trigeminal fibers, hot stimuli applied anywhere in this area evoked no response. The sensory phenomena in this area following resection of the sensory root of the trigeminal nerve, therefore, cannot be explained on the assumption that they are mediated solely through the facial nerve. Certain other findings, *e.g.*, the fact that light touch stimuli which when applied in the usual manner are not perceived are felt when a hair or a straw is swept across the skin, also suggest an afferent mechanism whose functions are more diffuse and totalized than those usually associated with peripheral nerves. According to Helson, the absolute zero of cutaneous sensitivity cannot be reached through section of the peripheral nerve supply (trigeminal and intermedius) but requires deletion of the sympathetic supply as well. In a study of patients with trigeminal neuralgia who had been treated by alcoholic injections of the Gasserian ganglion, patients with facial palsy due to lesions at various levels of the nerve, and patients who had been subjected to injury or extirpation of the cervical sympathetic on one or both sides, Carmichael and Woollard (1933) obtained no evidence that impulses subserving pain in the face or orbit are conducted centralward by nerve fibers other than components of the trigeminal nerve. Although these negative data fail to confirm Helson's findings they do not prove the latter erroneous.

On the basis of an analysis of the clinical results of various surgical procedures carried out in the treatment of atypical facial neuralgia, Fay (1932) advanced the opinion that afferent components both of the upper thoracic and vagus nerves extend into the cephalic region along the carotid arteries. This opinion has been confirmed by the results of experimental anatomical studies carried out on cats (Kuntz, 1934). After degeneration of the divided nerve fibers had taken place following extirpation of the superior cervical sympathetic and nodose ganglia, sections through the common, internal and external carotid arteries and the nerves closely associated with them still revealed intact nerve fibers. Marchi preparations of the common and internal carotid arteries following section of the roots of the upper four thoracic nerves just distal to the spinal ganglia revealed degenerated myelinated fibers in considerable numbers. On the basis of these findings it is evident that afferent components of the upper thoracic nerves join the plexus on the common carotid artery and extend cephalad along the internal and probably also along the external carotid artery. The presence of myelin degeneration in Marchi preparations of the nasal and nasociliary nerves following section of the roots of the upper four thoracic nerves (Christensen, 1934) indicates that some of the afferent components of the thoracic nerves which extend into the cephalic region reach the orbit and the nasal mucosa. The relationships of these fibers to the plexuses on the carotid arteries and their distribution in the cephalic area are illustrated diagrammatically in Figure 88. After degeneration of the divided fibers following extirpation of the entire cervical sympathetic trunk, including the superior cervical ganglion, but leaving the vagus nerve intact, sections of the internal and external carotid arteries and the nerves associated with them reveal numerous intact fibers obviously of vagus origin. These fibers probably are afferent components of the vagus with their cells of origin in the nodose ganglion.

The afferent spinal nerve components which extend into the cephalic region probably are not primarily pain-conducting fibers. Those which underwent myelin degeneration in the plexuses on the common and internal carotid arteries following section of the nerve roots, as observed in the Marchi preparations, are mainly fibers of larger caliber than the spinal

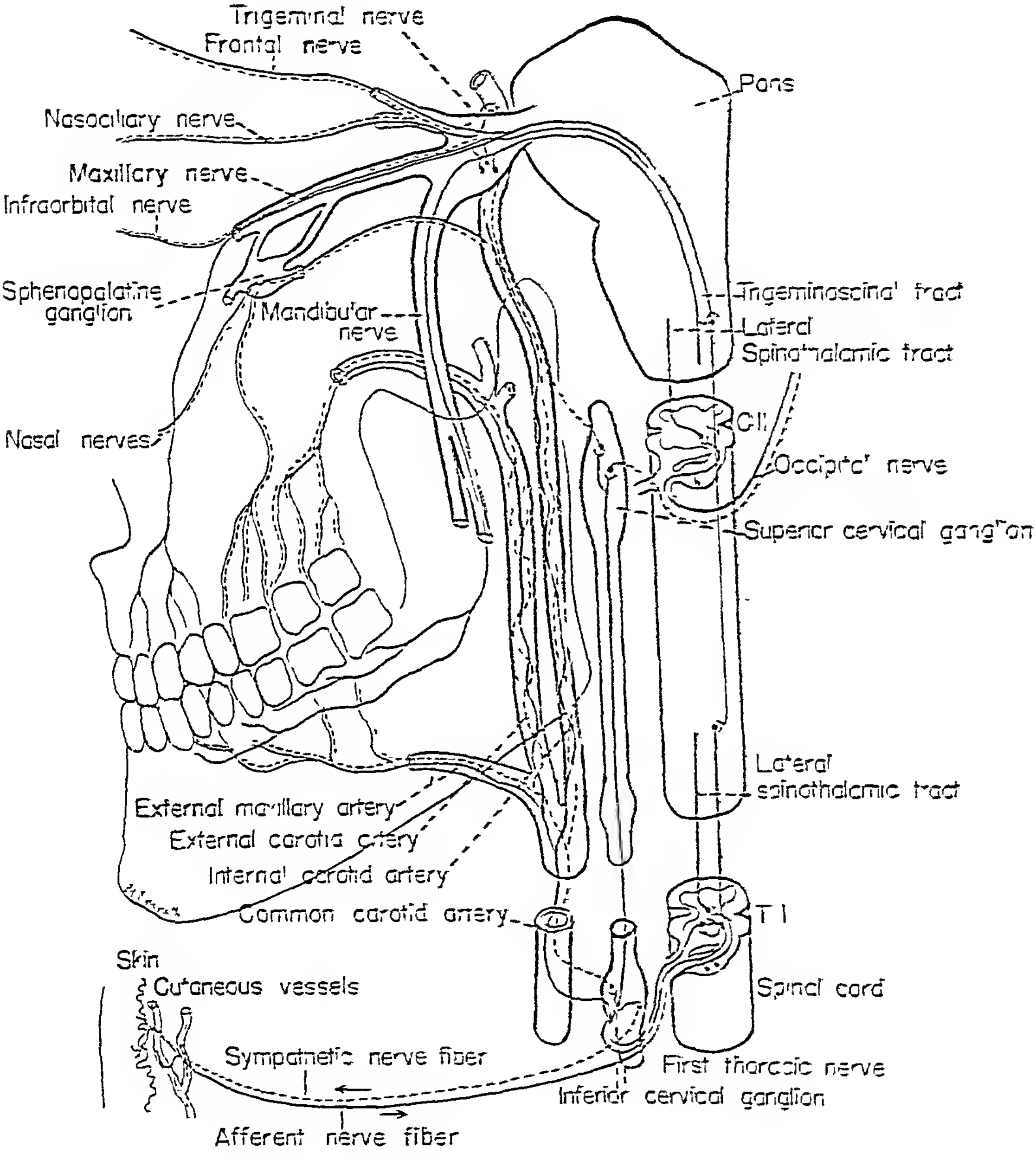


FIG. 88.—Diagrammatic illustration of the distribution of sympathetic nerve fibers and afferent components of the upper thoracic spinal nerves in the cephalic region via the plexuses on the common, internal and external carotid arteries and the probable conduction pathways involved in sensory and autonomic phenomena referred from cephalic lesions to the neck, upper thorax and upper extremities.

nerve fibers which are known to mediate pain. Mild electrical stimulation of the plexus on the common carotid artery, in our experiments, did not elicit pain reactions but resulted in reflex responses in the lower cervical and upper thoracic segments and particularly in the fore limb. The vagus components which join the plexus on the internal and external carotid arteries are mainly fibers of small caliber many of which are either unmy-

elinated or only thinly myelinated. Many of these probably are fibers which normally mediate pain.

Referred Pain.—Nature and Localization of Referred Sensations.—Under certain conditions, pain is localized, not at the site of its cause, but in another area which is supplied by nerves connected with the same segments of the central nervous system as those which supply the area in which the cause of the pain is located. Such pain is known as referred pain. Both the site of the cause and the area of reference may be either visceral or somatic but usually the referred pain associated with a visceral lesion is localized in a somatic area. Not infrequently visceral lesions give rise not to sensations which are distinctly painful, but to hyperalgesia or tenderness in the corresponding somatic area. The referred pain or hyperalgesia may accompany pain in the viscus which is the site of its origin or exist in the absence of true visceral pain. The area in which a referred pain is localized as determined by Head always falls within the range of distribution of the segmental nerves which supply afferent fibers to the site of the causative lesion. Such localization is not apparent in all cases, particularly if the causative lesion is located in deep somatic tissue. Data obtained by Inman and Saunders (1944) in an experimental study carried out on human subjects led them to conclude that a deep somatic lesion, such as injury to muscle, tendon or periosteum may give rise to pain which radiates along the pathways corresponding to the approximate segmental innervation of the deep somatic tissues. In contrast to the areas of skin innervation known as the dermatomes they have designated the segmental areas of skeletal innervation as the sclerotomes. In certain parts of the body, particularly the extremities and posterior cervical region, the latter do not coincide in spacial relationships to the corresponding dermatomes.

Nature of Visceral Lesions Which Are Commonly Accompanied by Referred Pain.—According to Ryle (1926), non-inflammatory visceral lesions rarely give rise to referred pain or somatic hyperalgesia unless they fall into the group of severe visceral crises. He regarded referred pain as less prevalent in visceral disease than current clinical conceptions seem to indicate. While the statements of patients regarding their own subjective symptoms cannot always be relied upon, certain gestures of the patient are significant. These, as a rule, do not apply to the somatic segment but to the area occupied by the visceral organs in question. In the case of anginal pain the patient not uncommonly places the clenched hand on the sternum as though to indicate that the pain has its origin in the aorta. The clenching of the hand undoubtedly implies the gripping character of the pain. Cardiac pain commonly is indicated by the flat hand in the left submammary area. The location of the pain of gastric ulcer not infrequently is indicated by placing two or three fingers in the mid-epigastric region or a little to the left of this. The pain of duodenal ulcer usually is localized at the right of the midline. In the case of renal colic, the patient grasps the back with the fingers toward the spine in the region of the kidney, indicating deep pain in the position of this organ. The pain associated with appendicitis and gall bladder disease usually is localized with remarkable accuracy unless inflammation or other gastro-intestinal lesions are associated with it. The position of a calculus in the ureter likewise can be localized quite accurately unless there is associated renal pain. Intestinal pain usually is localized less accurately, probably due to the changing

positions of the painful contractions Pain arising in the small intestine not infrequently is localized in the region around the umbilicus; pain arising in the large intestine usually is localized between the umbilicus and symphysis pubis but beneath the parietal peritoneum. Obstruction of the intestine at a fixed point, *e. g.*, the hepatic flexure, usually is localized with remarkable precision.

Referred pain is best demonstrated (1) in cases of severe visceral pain and (2) in association with inflammatory visceral disease. The pain which radiates into the arm in cases of angina pectoris, the subscapular pain of cholelithiasis and the testicular pain of ureteral colic are classical examples of the first group. Cutaneous hyperalgesia and muscular rigidity in the corresponding areas of the abdominal wall in cases of chronic gastric and duodenal ulcers are classical examples of the second group. These phenomena are associated mainly with diseases which involve organic changes in the viscera in question but rarely accompany functional diseases. For example, cutaneous hyperalgesia and muscular guarding rarely are associated with gastric pain due to extragastric causes. Pottenger (1931) reported hyperalgesia in the fifth to ninth thoracic segments due to pylorospasm brought about reflexly as a result of sigmoid diverticulitis. The subscapular pain of cholelithiasis may be due to cholecystitis as well as the presence of gall stones. It has been reported in cases of cholecystitis, in the absence of gall stones. In the presence of gall stones inflammation of the gall bladder can hardly be ruled out as a contributing factor in the referred pain. Testicular pain, according to Ryle, does not occur in ureteral colic unless the ureteral mucosa is inflamed or ulcerated. It may also occur in association with ureteral lesions in the absence of ureteral colic On the basis of extensive clinical observations, Ryle concluded that "visceral pain expresses a perturbation of visceral function (which may or may not be due to local organic disease) while the somatic phenomena generally express a structural lesion of the wall of the viscus."

In many cases of visceral disease, the somatic manifestations are not coincident with the visceral pain and may persist for some time after the visceral pain has subsided. Gastric ulcer not uncommonly is accompanied by tenderness, less commonly by superficial and deep hyperalgesia in the epigastric region, together with rigidity of one or the other rectus muscles and exaggerated abdominal reflexes on one side. These signs are most apt to be present if the patient has had a recent attack or is in pain at the time of the examination but, in many cases, they persist for days after the visceral pain has subsided in response to appropriate treatment. They cannot be directly attributed to the gastric contractions which are the cause of the gastric pain, although they may be reinforced by these contractions, but probably are due to a more or less constant flow of impulses from the site of the gastric lesion to the spinal cord from whence irradiation takes place along the nerves supplying the somatic segments in question. The somatic manifestations of gastric ulcer are more constant when the ulcer invades the muscle layers than when it involves only the mucosa. On the other hand, gastric carcinoma rarely is accompanied by somatic hyperalgesia or referred pain. This discrepancy probably is due to the fact that simple ulcer erodes the tissue and directly affects the sensory nerve endings in the muscles, while carcinoma invades the muscle by

growing between the muscle fibers. Simple gastritis rarely is accompanied by somatic signs (Ryle, 1926).

The referred manifestations of cholecystitis, whether occurring with or without gall stones, include superficial tenderness in the right upper quadrant of the abdomen, pain in the right subscapular and interscapular regions and tenderness over the middle dorsal spines and along the eleventh right rib. Muscular rigidity also may be present in the right upper abdominal quadrant in acute cases, and exaggeration of the abdominal reflex on the right side in subacute cases. The shoulder pain, commonly referred to as a sign of cholelithiasis, probably occurs only in cases in which the inflammation involves the diaphragmatic peritoneum, thus affecting the phrenic nerve directly, and in cases of diaphragmatic pleurisy.

Hyperalgesia and muscular rigidity in the lower right abdominal quadrant are frequent accompaniments of appendicitis, particularly of the inflammatory type. These have commonly been regarded as referred phenomena. Their superficial distribution conforms to the general principle of localization of referred pain as formulated by Head, i.e., the somatic area involved is supplied by the segmental nerves which also convey the visceral afferent fibers which supply the diseased viscus. In many instances appendicitis, particularly of the gangrenous type, is not accompanied by referred phenomena, although the onset of the disease is marked by severe visceral pain.

Certain investigators, particularly Morley (1931, 1937) have advanc experimental and clinical data which support the assumption that t sensory phenomena in the abdominal wall and the reflex muscular rigidi associated with appendicitis and various other lesions of the abdomina viscera do not depend on afferent impulses arising in the diseased viscu but are elicited by stimulation of somatic receptors in the parietal peri toneum overlying the diseased organ to which the inflammation has extended. Morley regards the superficial pain or hyperalgesia as due to peritoneo-cutaneous radiation, the muscular rigidity to peritoneo-muscular reflexes. In general every nerve which conveys sensory fibers to the parietal peritoneum also conveys sensory fibers to the corresponding cutaneous area and sensory and motor fibers to the underlying muscles. When the parietal peritoneum is irritated, according to Morley's hypothesis the pain radiates to the more superficial structures in the corresponding segments of the abdominal wall. Its localization consequently conforms to Head's principle of the localization of referred pains. This sensory radiation may be compared to the radiation of pain from a carious tooth to adjacent teeth or the skin of the face. Irradiation within the central nervous system known to be associated with spinal reflex activity may be a factor in this process. According to this point of view the somatic pain or tenderness associated with appendicitis is not a referred sensory phenomenon in the ordinary sense. Pain localized in a somatic area due to other visceral lesions from which the inflammatory process extends to the parietal peritoneum or the parietal pleura obviously falls into the same category unless the sensory phenomena in the somatic area can be demonstrated in the absence of parietal involvement in the inflammatory process.

Morley regards the pain in the area of distribution of the descending branches of the third and fourth cervical nerves, caused by stimulation of

the abdominal surface of the central area of the diaphragm as comparable to the superficial pain caused by irritation of any other area of the parietal peritoneum. Since the afferent components of the phrenic nerves are essentially somatic, the shoulder pain caused by phrenic stimulation does not involve viscero-somatic sensory radiation. This phenomenon nevertheless conforms to the current concept of referred pain. It differs from the phenomenon of referred pain associated with certain cardiac lesions only in that the afferent conductors from the diaphragm may be classified as somatic afferent nerve components, whereas those from the heart or coronary vessels are essentially visceral

True cardiac pain is a relatively rare symptom of cardiac disease. It is less common in valvular disease and obvious hypertrophy or dilatation of the heart than in purely functional derangements. It is localized in the submammary area and sometimes is accompanied by cutaneous hyperalgesia in the precordial region The deep pain of angina pectoris commonly is localized in the sternal region, the referred pain may be localized in the upper left thoracic area, along the inner side of the left arm to the elbow or wrist or even to the fingers and more rarely in the right arm, neck and jaw The segments particularly involved are supplied by the lower cervical and upper two or three thoracic nerves. The afferent fibers supplied to the first part of the aorta and coronary arteries via the sympathetic trunk also are components of the upper thoracic nerves The pain caused by coronary occlusion, according to Katz, Wayne and Weinstein (1935), is due to direct stimulation of afferent nerve fibers, since it does not follow occlusion in a segment of the artery stripped of its nerves

Myocardial infarction not infrequently is followed by persistent pain in one or both shoulders, which varies in severity from the clinical picture of periarthritis with intense pain and marked limitation of motion to one of mild aching pain with a sensation of weakness but no limitation of motion. These symptoms, which occur more commonly in the left shoulder than in the right, may persist for several weeks or months In attempting to explain them, Ediken and Wolferth (1936) suggested an analogy to the causalgia which sometimes follows obliteration of a peripheral artery. Boas and Levy (1937) advanced two hypotheses. (1) pain radiating from the heart to a shoulder in which slight painful stimulation is already present might, by summation, cause more intense pain; (2) impulses of pain conducted from the heart might result in sensitization of the neurons whose fibers make up the brachial plexus. Ernstene and Kinell (1940) advanced the opinion that the symptoms arise as a result of relative disuse of the shoulder and abnormal tension of the shoulder muscles Pain once developed in the shoulder would tend to keep the muscles tense. The last hypothesis seems the more probable since a patient who has suffered acute coronary thrombosis limits the use of the shoulder muscles and may unconsciously keep the muscles of the shoulder girdle on one or both sides in a state of abnormal tension for a relatively long time. The continued muscle tension would explain the prolonged duration of the symptoms in many patients. While these hypotheses may be helpful, it must be admitted that the data available do not afford an adequate basis for a complete explanation of the mechanism responsi [illegible] persistent shoulde pain associated with myocardial infarction.

The testis is exquisitely sensitive to pa [illegible] ion. In a serie

experiments involving nerve block, Woollard and Carmichael (1933) have demonstrated that when both the posterior scrotal and genitofemoral nerves are blocked, pain is no longer localized in the testis but is felt in the tenth thoracic segment on the same side. This finding is peculiarly significant since it indicates that reference of pain which has its site of origin in the testis may be obtained when the only pathway for the conduction of afferent impulses from the viscus consists of the nerve fibers associated with the spermatic artery, i. e. the reference is independent of a somatic nerve supply to the viscus.

Dental lesions and lesions of the nasal and paranasal mucous membranes frequently give rise to pain in areas other than the site of the lesion but within the area of distribution of the trigeminal nerve. These phenomena may be regarded as comparable to the association of superficial pain with irritation or inflammation of the parietal peritoneum or the parietal pleura. Lesions in the same locations sometimes give rise to pain localized outside the area of distribution of the trigeminal nerve. Pains referred to the ear from various lesions including temporomandibular arthritis, inflammation of the paranasal sinuses, tonsillitis, carcinoma of the tongue, pharynx or larynx, meningitis, etc. are not uncommon (Watson-Williams, 1932, 1933). Dental lesions also give rise to sensory disturbances referred to the ear and other areas outside the limits of trigeminal distribution. Among the latter, Main (1938) has reported chronic otalgia and other symptoms referable to the ear, such as tick-like noises, sensations of pressure in the suboccipital region, numbness associated with ischemia and pain in the arm and hand, etc. In many of his patients the particular syndrome observed which frequently included headache and other sensory trigeminal disturbances had been of long standing. In most of them extraction of the offending tooth resulted in permanent relief of the symptoms. Henry (1935) reported headache in the occipital or parietal region as a frequent symptom associated with lesions of the third molar. Some of these complications of dental lesions, obviously, are referred phenomena which conform to Head's theory of the localization of referred pains in all essential details. Others exhibit characteristic features of referred phenomena but conformation to Head's theory of localization is less obvious (Kuntz and Main, 1940).

Lesions in the orbit, the mucous membranes of the nose and paranasal sinuses and in the mastoid area not infrequently give rise to referred pains in the neck, shoulder, arm, forearm and hand. This condition was first described by Sluder and has become quite generally recognized as a clinical syndrome. A typical case of this kind in which a lesion in the mastoid area gave rise to pain referred to the face, neck, upper extremity and chest which subsided with the healing of the lesion has been reported recently by Schugt (1944). In some instances the pain is accompanied by other referred phenomena. For example, Ferracol (1932) cited a case in which operation for the relief of nasal obstruction was followed by eruption on the chest and another in which dressings of the wound following a mastoid operation caused violent pains in the arm and eruptions on the chest. The afferent fibers through which the impulses which elicit the referred phenomena in these instances are conducted from the causative lesions undoubtedly are components of the upper thoracic nerves which traverse the inferior cervical sympathetic ganglion and ascend along the common and internal carotid arteries (Kuntz, 1936). These fibers, due to their anatomical

relationships, may be classified with the visceral afferent components of the spinal nerves (Fig. 88). Phenomena other than those which are essentially sensory which are referred to thoracic segments from cephalic lesions, such as the eruption on the chest cited by Terracol, undoubtedly involve reflex sympathetic excitation elicited by impulses which arise at the site of the lesion and are conducted into the spinal cord through the afferent fibers in question.

Careful analysis of the manifestations of pathologic lesions in still other visceral organs would reveal visceral pain in some cases unaccompanied by referred somatic hyperalgesia or pain, and in others accompanied by these phenomena, together with muscular guarding or rigidity. The absence or presence of somatic manifestations probably depends mainly on the nature of the visceral lesion, and is not necessarily an indication of the severity of the disease.

In an experimental investigation carried out on human subjects, in which cephalic pain was produced by irritation of deep structures in the cervical and basi-occipital segments, particularly the periosteum and the periarticular tissues, Campbell and Parsons (1944) found that this pain resembled the symptomatic head pain characteristic of certain post-traumatic clinical states. Irritation in the occipito-atlantal condylar region and the first cervical interspace posteriorly constantly resulted in pain localized in the cephalic region, predominantly in the occipital area but with considerable reference to the forehead. Irritation of the cervical interspinous ligaments from the second to the fifth interspace resulted in pain predominantly in the occipital and upper cervical regions with only occasional reference to the frontal area. These pains were accompanied by autonomic disturbances such as pallor, sweating, pulsus alternans, nausea, etc., which varied in intensity, extent and duration with the amount of stimulation and the degree of preëxperimental pathology. The resemblances both of the subjective experiences and the objective signs to those of certain non-traumatic "neuralgias" and "myalgias" of the occipito-cervical-facial regions were striking.

The radiation of pain into the occipital area from lesions in deep structures in the posterior cervical region may be explained on the basis of the morphology and functions of the sacrospinalis muscles and their innervation. Irritation in any segment, but particularly in the cervical ones, may result in traction on the occipital attachments of these muscles, giving rise to pain in that area. Cephalic pain and its concomitants associated with thoracic and even lumbosacral lesions may be explained on the same basis. The muscles involved in balancing the cranium upon the vertebral column, including the trapezius, sternocleidomastoid and a deep suboccipital group comprising the anterior, lateral and posterior recti and the superior and inferior obliques, like some of the external muscles of the cranium, are derived from cervical, occipital and branchial myotomes. Their motor innervation, consequently, is derived from cervical segments of the spinal cord and from the brain stem. Sensory impulses arising in these muscles, their associated sclerotomal tissues and the overlying integument predominantly reach the two upper cervical spinal cord segments via the trigeminospinal tract. The sensory innervation of these structures, therefore, is related segmentally to that of the upper cervical myotomes; consequently,

reference of pain into the cephalic region from deep cervical lesions is not incompatible with Head's theory of localization.

Theories Regarding the Mechanism of Referred Pain.—Among the early investigations carried out in attempts to explain the mechanism of referred pain, those of Lange (1871–1876), Ross (1888), Head (1889) and Faber (1899) deserve special mention. The theory which has commanded the most universal attention is that of Mackenzie (1910) which is essentially an elaboration of the theories of Lange and Ross. Like the earlier investigators named above Mackenzie regarded the sensory manifestations of visceral disease which are localized in somatic areas as reflex phenomena and designated them "viscero-sensory" reflexes. These he explained on the basis of hyperirritability in the corresponding segments of the spinal cord due to exaggerated visceral stimulation. According to his view irritation of a visceral organ sets up an exaggerated flow of nerve impulses which enter the corresponding segments of the spinal cord and give rise to an irritable focus in which the threshold of stimulation is reduced to such an extent that the normal impulses arising in the skin, muscles and other peripheral structures give rise to painful sensations which are referred to the periphery in the somatic segments in question. He assumed that when any portion of the spinal cord has become hyperirritable due to excessive stimulation caused by visceral disease it may remain so for some time during which the threshold for stimulation for all the nerves connected with this portion of the cord is lowered. Both the somatic pain or hyperalgesia and the muscular rigidity associated with visceral disease according to Mackenzie's theory are expressions of the hyperirritability in the spinal cord, the pain or hyperalgesia being produced by viscero-sensory reflexes, the muscular rigidity by exaggerated viscero-motor reflexes. In the light of present physiologic knowledge the expression viscero-sensory reflex as employed by Mackenzie must be regarded as unfortunate since the hypothetical phenomenon in question is not of the nature of a reflex. His concept of irritable foci in the central gray matter undoubtedly expresses the phenomenon of irradiation now well known to physiologists and regarded as one of the properties of reflex arcs.

Szenizo (1927) advocated the theory of Mackenzie in a slightly modified form. He assumed that the visceral afferent fibers at least in part terminate in the posterior cell column in the spinal cord in relation to neurons which are related to the spinothalamic system and that it is mainly the hyperirritability of these cells due to excessive visceral stimulation which explains the phenomenon of somatic hyperalgesia in visceral disease. As long as the threshold of stimulation of these cells for peripheral impulses remains sufficiently low the slightest stimulation of the peripheral pain conducting fibers in the somatic segments in question may elicit painful sensations whose intensity is disproportionate to the intensity of the peripheral stimulus. Under certain conditions pain may be felt in the corresponding somatic segments even in the absence of appreciable somatic stimulation. On this basis, somatic hyperalgesia associated with visceral disease in the absence of visceral pain must be regarded as due to hyperexcitation of the spinal cord cells in question through a flow of visceral impulses whose intensity is below the threshold for visceral pain (Goldscheider, 1923). The lingering somatic hyperalgesia which not infrequently

remains after the visceral pain has subsided. in cases of visceral disease, could be explained on the same basis.

The data advanced by Morely (1931), already referred to, seem to be incompatible with any theory based on the assumption that the referred phenomena associated with visceral disease are referred directly from the diseased viscus. According to his interpretation. they seem to support the assumption that the afferent impulses involved in the production of the somatic pain and other somatic phenomena associated with lesions of the abdominal viscera arise. not in the diseased viscus, but in the parietal peritoneum; consequently, they are conducted centralward through somatic afferent nerve fibers. He regards the phenomena of deep and superficial pain or tenderness and muscular rigidity of the abdominal wall associated with inflammatory disorders in the abdomen as brought about through two closely related mechanisms. "peritoneo-cutaneous radiation" and the "peritoneo-muscular reflex." These mechanisms presuppose irritation or inflammation of the parietal peritoneum. According to this theory, the pain produced by stimulation of the parietal peritoneum radiates to the superficial structures and is not appreciated as arising in the parietal peritoneum at all. The muscular rigidity is a purely somatic reflex response to stimulation of the parietal peritoneum.

The phenomena described by Morley undoubtedly occur in cases in which visceral inflammation extends to the parietal peritoneum. The reflex muscular guarding or rigidity which accompanies somatic hyperalgesia or pain in many cases of visceral disease, *e. g.*. acute appendicitis. can be explained most satisfactorily on this basis. The muscular response. furthermore, may be regarded as a contributing factor in the production of the associated hyperalgesia. muscle tenderness and pain. Since painful stimuli are the most provocative causes of reflexes. acutely tender muscles tend to remain permanently contracted. This tendency undoubtedly is an important factor in the maintenance of muscular rigidity. in many cases, after the visceral inflammation has subsided. As long as the muscle remains in a sufficiently high state of tonus it also remains hypersensitive.

The referred phenomena, including pain, associated with carious teeth and certain other lesions in the region of the mouth and pharynx. like the muscular rigidity and tenderness caused by irritation of the parietal peritoneum, involve no visceral afferent fibers. Referred pains in certain other instances, *e. g.*, pain referred to the knee due to a lesion in the region of the hip joint, involve afferent conduction only through somatic fibers.

The data available regarding the referred phenomena associated with purely visceral lesions do not warrant the conclusion that these phenomena in all cases of visceral disease can be explained on the assumption that the afferent impulses involved in their production are conducted centralward through somatic nerve fibers. For example, stimulation of the testis, as has been pointed out by Woollard and Carmichael (1933). may give rise to pain which is referred to the appropriate somatic area in the absence of functional somatic afferent fibers to this viscus or adjacent tissues. The referred phenomena associated with angina pectoris likewise cannot be explained on the assumption that the afferent impulses involved are conducted centralward through somatic fibers. These impulses undoubtedly arise in the walls of the heart or coronary arteries and are conducted into the spinal cord through visceral afferent fibers.

The assumption that muscle spasm or rigidity associated with visceral disease is due in all cases to stimulation of somatic afferent fibers by irritation or inflammation of a serous membrane excludes consideration of the easily demonstrable fact that irritation of a visceral organ may elicit reflex contraction of skeletal muscles (viscero-skeletal reflex). This reaction may be demonstrated following high transection of the spinal cord which eliminates the higher reflex mechanisms and intentional contraction. Whenever muscular rigidity or hypertonus arises in association with visceral disease it may be a factor in the development and maintenance of the associated pain or hyperalgesia.

Effects of Autonomic Nerves on Sensory Threshold.—Data which seem to indicate that the sensory threshold in any given area may be altered by the effect of impulses conducted through the autonomic nerves are not wanting. In an experimental study involving measurements of the excitability of somatic sensory nerves by determination of their chronaxia Foerster, Altenburger and Kroll (1929) and Altenburger and Kroll (1930) found that stimulation of the sympathetic trunks or the injection of adrenin raises the sensory threshold, a phenomenon in complete accord with the experience of diminished sensation of pain in emotional states such as anger and fear. On the other hand, the threshold of cutaneous sensory stimulation may be distinctly lowered following sympathectomy or the administration of parasympathomimetic drugs such as choline and pilocarpine. For example, Pette (1927) reported paresthesia of the corresponding cutaneous area following sympathectomy, and Fulton (1928) observed increased cutaneous sensitivity in the lower extremity following lumbar sympathectomy. These observations corroborate the early finding of Claude Bernard (1851) that the skin of the face and ears of rabbits and cats exhibits hyperesthesia following superior cervical ganglionectomy. In experiments reported by von Brücke and Yamagiwa (1936) the threshold of sensory stimulation of the phrenic nerve was raised following section of the cervical sympathetic trunk on the same side.

Certain individuals, as has been pointed out by Scrimger (1930), undoubtedly may train themselves to perceive as pain afferent impulses of visceral origin which do not ordinarily reach the sensory level. Continuous or recurring pain also may increase its actual perception. Intense pain in any part of the body, according to Hardy, Wolff and Goodell (1940), may raise the threshold of painful stimulation in other parts as much as 35 per cent, as measured by their method of determining pain thresholds in the skin by thermal radiation. As reported by White and Smithwick (1941), Chapman found no evidence that the sympathetic nerves exert an influence in this elevation of the sensory threshold. In testing the cutaneous sensitivity of patients before and after sympathectomies of various types he found no alteration in sensory acuity. He could furthermore demonstrate no alteration in the sensory threshold after injection of adrenin or acetyl-beta-methylcholine chloride. These data fail to support the finding of Davis and Pollock (1932) that stimulation of the sympathetic nerves extending from the superior cervical sympathetic ganglion into the head gives rise to pain due to the effect of the peripheral response to such stimulation on sensory receptors and the conclusion of Pollock and Davis (1935) that the effects of sympathetic reflex activity in the shoulder region

elicited by phrenic nerve stimulation, play a causative rôle in the shoulder pain resulting from faradic stimulation of the diaphragmatic peritoneum.

Sympathetic Reflex Phenomena Associated With Referred Pain.—The theories outlined above afford plausible explanations of the mechanism of referred pain but they do not adequately take into consideration the viscero-cutaneous and viscero-motor reflex phenomena which probably are invariably associated with somatic hyperalgesia, such as vasoconstriction, perspiration and pilo-erection. These phenomena are particularly marked in certain cases.

Wernoe's (1920–1925) clinical and experimental studies have contributed much to our knowledge of reflex viscero-cutaneous and viscero-motor reactions to visceral stimulation in relation to the sensory phenomena involved in referred somatic hyperalgesia. He observed clinically that cutaneous hyperalgesia commonly is accompanied by cutaneous ischemia, due to peripheral vasoconstriction, and that the area of cutaneous ischemia, in general, coincides exactly with the area of cutaneous hyperalgesia. In certain cases, he also observed localized cutis anserina in the hyperalgesic area. In his experience, cutaneous ischemia was so constantly present in areas of hyperalgesia associated with visceral disease that he was able to use it as a diagnostic character, being able, in many cases, to recognize the hyperalgesic area by virtue of the cutaneous ischemia when it would have been difficult or impossible to demonstrate hypersensitivity by the more usual methods. On the basis of these findings, Wernoe concluded that cutaneous hyperalgesia probably does not depend on the effect of visceral stimulation of neurons in the spinal cord but has its origin in changes brought about in the skin through viscero-cutaneous reflexes. In support of this conclusion from the clinical side, he pointed out that under certain conditions sympathetic stimulation alone gives rise to pain. For example, if the fingers are subjected to cold they gradually become ischemic and painful until, with complete anemia, the anesthetic stage is reached. If the hand is then warmed, the fingers again become painful until circulation is restored to normal. As the fingers are subjected to cold, vasoconstriction is brought about through reflex stimulation of the vasomotor fibers. The consequent pain is the result of the stimulation of pain receptors caused by the ischemic condition of the surrounding tissues and the hypertonic state of the smooth muscle in the vessel walls. In like manner, he assumed that the cutaneous pain receptors may be stimulated as a result of the ischemia brought about in the skin through viscero-cutaneous reflexes.

The vasoconstriction due to hypertension or spastic contraction of the smooth muscle in the vessel walls or the consequent ischemia of the adjacent tissue undoubtedly is a major factor in the production of pain referable to the blood vessels. Peripheral vasoconstriction elicited reflexly through the sympathetic innervation of the blood vessels in a somatic area by impulses arising in a diseased viscus, therefore, may be regarded as a contributing factor in the production of hyperalgesia in the same area. Reflex contractions of the erector pili muscles, elicited in the same manner, likewise may well be regarded as a contributing factor in the hypersensitivity of the area involved, particularly to light touch and even air currents playing on the skin.

Davis and Pollock (1932, 1935, 1936) have supported a similar point of

view. On the basis of experimental and clinical data, outlined in the preceding pages, which seem to support the assumption that stimulation of the sympathetic nerves which supply a peripheral area results in changes in that area which exert a direct stimulating effect on the pain receptors, they have advanced the opinion that sympathetic stimulation may be a causative factor in the production of pain. They have furthermore regarded the abolition of referred pain by anesthesia of the area in which it is localized (Weiss and Davis, 1929, Morley, 1929, Rudolf and Smith, 1930) as indicating that the pain felt in that area due to a visceral lesion or stimulation of the appropriate afferent nerves is caused by stimulation of the peripheral pain receptors. In view of these considerations and the evidence of reflex activity mediated through the sympathetic nerves in the somatic area in which the referred pain associated with a visceral lesion is localized, they have supported the assumptions that this reflex activity represents the major factor in the causation of the pain in the somatic area and that the impulses generated at the periphery are conducted centralward via the somatic pain conducting pathways.

Many of the data which have been interpreted as supporting this point of view seem to be unequivocal. In 25 patients with well marked pains definitely localized in somatic areas but due to visceral diseases including angina pectoris, pleuritis, carcinoma of the esophagus, gastric ulcer, cholecystitis, nephrolithiasis, acute appendicitis, salpingitis and pyelitis reported by Weiss and Davis (1929) the pain either was abolished or greatly alleviated by infiltration of the painful cutaneous areas with a 2 per cent solution of novocaine. They also reported the abolition, by the same means, of referred pains induced experimentally in two normal subjects by distention of a segment of the duodenum or the distal portion of the esophagus by inflation of a rubber balloon. Similar observations have been reported by Davis and Pollock (1936). In a number of patients in whom a phrenic exeresis was being carried out, faradic stimulation of the phrenic nerve in the neck resulted in pain which was always referred to the trapezius ridge or the supraclavicular region. When this cutaneous area was anesthetized the same stimulation no longer resulted in pain.

The cutaneous area in which the referred pain is localized does not include the entire area supplied with afferent fibers which enter the spinal cord segments from which the viscus in question is innervated. In experiments reported by Bowden and Rigler (1934), anesthesia of the circumscribed area in which a referred pain was localized abolished the pain in that area but it was felt in a position outside of it. If the referred pain associated with a visceral lesion is felt only near the midline and this area is anesthetized, as observed by Wilkinson (1937), the pain moves lateralward in the same segments, due to the fact that pain is felt only in the area in which it is most intense.

The data outlined above are not incompatible with the theory that impulses may be generated in peripheral pain receptors as a result of sympathetic reflex activity elicited by visceral afferent stimulation. Reflex responses at the periphery which are elicited through either sympathetic or somatic efferent pathways by afferent stimulation at the site of a visceral lesion undoubtedly play a role in the referred pain or hyperalgesia associated with the visceral disease, particularly when the referred phenomena

develop slowly and persist even after the visceral stimulation has subsided These factors obviously play no significant rôle in the production of the referred pain in certain instances. For example, the pain referred to the tip of the shoulder due to stimulation of the diaphragm usually arises almost instantaneously In some instances, furthermore, it is not abolished by anesthetizing the cutaneous area in which it is localized (Woollard and Roberts, 1932). In order to test the hypothesis that shoulder pain elicited by phrenic nerve stimulation may be abolished by anesthetizing the cutaneous area in which the pain is localized, Livingston (1938) carried out clinical experiments as follows: In a patient with a subphrenic abscess, shoulder pain was elicited by touching the dome of the diaphragm with the tip of a uterine probe inserted through the incision made for the purpose of draining the abscess The shoulder area was then infiltrated widely with a 1 per cent solution of novocaine and the stimulation of the diaphragm repeated. In every instance the patient complained of pain in the shoulder the instant the diaphragm was stimulated and localized it within the novocainized area to which the pain had been originally referred. These results seem to preclude stimulation of pain receptors in the skin, due to the effects of reflex activity mediated through either sympathetic or somatic nerves, as a causative factor in the production of the referred pain.

Data obtained in an experimental study of referred pain due to intramuscular stimulation, as reported by Kellgren (1938), seem to support the assumption that this pain is associated with referred tenderness of the deep structures. Its distribution conforms to a spinal segmental pattern which differs somewhat from that of the segmental innervation of the skin. It is always diffuse and is not abolished by anesthesia of the region in which it is localized; consequently, it is independent of any reflex mechanism involving stimulation of pain receptors in the area of reference. The pain appears to be referred, not to the skin, but to deep structures and may be confused with pain arising in the latter This seems to support the assumption that the impulses responsible for pain from muscle and from other deep structures may be conducted in a common central pathway. The diffuse character of the referred pain, according to Kellgren, may be explained on the assumption that the fibers which conduct impulses of pain from muscle have diffuse connections within the central nervous system.

The reflex phenomena associated with referred pain and hyperalgesia constitute a significant feature of the total clinical picture but, in view of all the data available, they cannot be regarded as adequate to account for causation of the referred sensory phenomena. A complete understanding of the mechanism of referred pain must await further investigation. Irradiation probably is an essential factor in the production of the somatic pain caused by visceral stimulation

The assumption that the gray matter in the spinal cord segments into which the afferent impulses arising at the site of the causative lesion are conducted plays a major rôle in the production of the referred phenomena, as implied in the original Lange-Ross theory and Mackenzie's elaboration of this theory, still affords the most helpful point of view The concept of irradiation in the spinal gray matter, substituted for Mackenzie's concept of "irritable foci," undoubtedly will be incorporated in any adequate

theory of the mechanism of referred pain The physiologic concepts of summation, facilitation and inhibition also are applicable, since afferent impulses emanating from the site of a lesion giving rise to referred pain impinge upon a central neuron pool which also receives impulses from the peripheral area in which the referred phenomena are localized Facilitation and inhibition undoubtedly play a role in the reflex phenomena associated with referred pain The summation of visceral and somatic afferent impulses probably is essential for the production of referred pain in certain instances, as suggested by the abolition of the pain in the somatic area by cutaneous anesthesia In other instances, particularly those in which the referred pain is not abolished by cutaneous anesthesia, summation seems to be unessential

CHAPTER XX

AUTONOMIC IMBALANCE

The Concept.—Genesis and Definition.—The visceral organs, with certain exceptions, are innervated through both the sympathetic and the parasympathetic divisions of the autonomic nervous system, which are synergistic in function; consequently, any disturbance of the functional balance of the sympathetic and parasympathetic nerves must result in visceral dysfunction in some degree. Von Noorden recognized this as early as 1892 and called attention to various clinical conditions associated with increased vagus irritability which he designated vagus neuroses. The clinical concepts of vagotonia and sympatheticotonia were first formulated by Eppinger and Hess in 1909 and further elaborated by them in a series of later papers. In many individuals in whom adrenin produced strong sympathetic stimulation, according to their findings, pilocarpine failed to stimulate the parasympathetic nerves and atropine did not paralyze them. In other individuals in whom pilocarpine or atropine produced a strong parasympathetic reaction, they found that the injection of adrenin resulted in no apparent effect on the sympathetic nerves. On the basis of extensive observations on the effects of these drugs in man, they concluded that all persons who react strongly to pilocarpine and atropine are relatively insensitive to adrenin, and all persons who react strongly to adrenin are relatively insensitive to atropine and pilocarpine. On the basis of this conclusion, they classified clinical cases exhibiting a functional imbalance between the sympathetic and parasympathetic nerves as vagotonic or sympatheticotonic, depending on the relative reactivity of the parasympathetic and sympathetic nerves. They recognized more or less definite symptom-complexes which usually are associated with exaggerated reactivity of the parasympathetic and sympathetic nerves respectively. According to their original theory, absolute vagotonia is characterized by actual hyperreactivity or exaggerated tonus of the parasympathetic nerves; absolute sympatheticotonia by hyperreactivity or exaggerated tonus of the sympathetic nerves. They conceded that relative vagotonia may exist in the absence of exaggerated parasympathetic tonus if the reactivity of the sympathetic nerves is subnormal or there is a deficiency in the chromaffine system and that relative sympatheticotonia may exist in the absence of exaggerated sympathetic tonus if the reactivity of the parasympathetic nerves is subnormal. In either case, vagotonia and sympatheticotonia involve an increase in functional activity in the respective division of the autonomic nervous system which may affect the entire division or only a portion of it.

According to the original theory of Eppinger and Hess, the entire sympathetic and parasympathetic divisions of the autonomic nervous system are tonically stimulated and sustain a physiological balance which may be shifted in favor of one or the other division by abnormal functional conditions. Exaggerated tonus of either system does not necessarily imply hyperirritability of the nerve centers involved but may be brought about

by an excess of stimulating substances in the blood. In general, they regarded vagotonia as characterized by hyperreactivity to parasympathetic stimulation and sympatheticotonia as characterized by hyperreactivity to sympathetic stimulation of all the organs innervated through the autonomic nerves, although they recognized the possibility of localized vagotonia.

Critique.—On the basis of an extensive study of the effects of adrenin, pilocarpine and atropine in clinical conditions, Petrén and Thorling (1911) pointed out that, in certain diseases in which exaggerated parasympathetic tonus usually is apparent, *e. g.*, gastric and duodenal ulcer, bronchial asthma, etc., a small percentage of the patients, as judged by their reactions to these drugs, exhibits exaggerated sympathetic tonus and a somewhat larger percentage reacts strongly to adrenin and also to pilocarpine and atropine, thus proving that the same individual may exhibit heightened reactivity of both divisions of the *autonomic* nervous system. They, therefore, suggested that the observed reactions to parasympathomimetic and sympathomimetic drugs can be explained most satisfactorily, in certain cases, on the assumption of heightened irritability of both the parasympathetic and the sympathetic nerves, but agreed with Eppinger and Hess regarding the existence of vagotonia and sympatheticotonia as recognizable functional states which represent deviations from the normal functional balance between the parasympathetic and the sympathetic nerves.

The findings of Petrén and Thorling cited above have been confirmed by not a few later investigators. It also has been amply demonstrated that the symptom-complexes commonly associated with certain diseases which, according to the theory of Eppinger and Hess, are related to vagotonia also include symptoms which suggest exaggerated reactivity of the sympathetic nerves. Symptom-complexes associated with diseases which, according to this theory, are related to sympatheticotonia likewise also include symptoms which suggest hyperreactivity of the parasympathetic nerves. For example, the dominant symptoms of pulmonary tuberculosis, particularly during the second and third stages of the disease, usually indicate vagotonia, yet the gastro-intestinal symptoms sometimes suggest exaggerated sympathetic tonus. The dominant symptoms of hyperthyroidism, such as tachycardia, increased metabolism, fever, etc., likewise suggest sympatheticotonia, yet gastro-intestinal hypermotility, so common in this disease, involves exaggerated parasympathetic reactivity. Unusually strong reactions to either parasympathomimetic or sympathomimetic drugs or both also have been reported repeatedly in certain individuals apparently in good health who exhibited no objective evidence of a functional autonomic imbalance.

The symptom-complex commonly associated with hyperthyroidism frequently has been cited as incompatible with the theory of vagotonia and sympatheticotonia. According to Eppinger and Hess, patients with exophthalmic goiter may be classified as vagotonic or sympatheticotonic on the basis of gastro-intestinal hypermotility and tachycardia, respectively. Many cases of exophthalmic goiter, as is now well known, exhibit both gastro-intestinal hypermotility and tachycardia at the same time, consequently, it cannot be assumed, on the basis of these symptoms, that either vagotonia or sympatheticotonia exists in these cases. In many cases of this disease the dominant symptom-complex, including persistent diarrhea, gastric hyperacidity, vomiting, vasodilatation, and circum-

scribed edema, strongly suggest parasympathetic hyperirritability, but absolute vagotonia or sympatheticotonia, in the sense of Eppinger and Hess, probably never is observed in cases of exophthalmic goiter.

One of the most striking symptom-complexes indicative of general parasympatheticotonia is that associated with spastic constipation which has been regarded by most investigators in this field as a purely parasympatheticotonic disease (Muller, 1924; Bernhold and Hauptstein, 1928). In a study of frank cases of spastic constipation, in which the pupillary reaction was used as an index, Bernhold and Hauptstein (1928) observed the expected parasympathetic response to pilocarpine and atropine in ... case.

Kraus and Zondek (1922, 1924, 1928) have forcibly called att... the influence of electrolytes on the autonomic nerves and emph... importance of the acid-base balance in all diseases in which the ... system is directly involved. According to their point of view ... activity results in diminution of the calcium concentration ... membrane. This diminution of calcium is accompanied by a... in intracellular potassium, an increase in the permeability of th... hydration of its protoplasm. Cellular inactivity, on the ot... results in a relative increase in the calcium concentration of the ... brane, a decrease in the permeability of the cell and dehydr... protoplasm. Potassium and calcium concentrations respecti... fore, are indicative of cellular activity and cellular rest. Since t... changes may be initiated by nerve impulses, the concentrati... potassium or calcium in the serum may be an index of cellular ... the serum levels do not necessarily change the reactions ... Changes in the ionic concentration, however, not infrequently ... changes in the autonomic balance.

Since the assumption that sympathetic and parasymp... tonus is associated with ionic concentration is based mainly o... to the injection of adrenin, observed in clinical cases, it i... inquire into the validity of this criterion. Jendrassik an... found no constant correlation between the reaction to a... K/Ca ratio in the blood. Brems (1927) also found ... general rule. In experiments reported by Petersen and L... carried out on normal men and clinical patients, individ... basis of their reactions to adrenin, were classified as frank... tonic exhibited a lower K/Ca ratio than individuals who, o... were classified as frankly vagotonic, but they also fou... this rule.

The lack of constancy in these experimental results ... the importance of the ionic balance in relation to the ... between the sympathetic and parasympathetic nerv... ratio in the body fluids is not a true index of the ionic ... cell membranes, on which the reactions of the cells de... Levinson have demonstrated experimentally that ... liberates calcium and takes up potassium ... responding to the time of vasodilatation ... presumptive vagotonic status of the ... used to denote a condition of tissue ... increased permeability, the calcium ...

the potassium diminished, i. e., the vagotonic person should have a low K/Ca ratio, the physiologic effects being modified by differences in ionization. The vagotonic person, as clinically defined, does not exhibit increased metabolism with capillaries dilated and permeable but, on the contrary, exhibits decreased metabolism and reduced capillary permeability.

Inasmuch as the terms vagotonic and sympatheticotonic, as clinically defined, do not necessarily represent the functional states of the tissues, Petersen and Levinson have suggested that this classification be discarded. They have introduced and defined the terms "parasympathetic status" and "sympathetic status." The former, according to their definition, denotes capillary dilatation, tissue activity, calcium dissimilation and hydration, the latter, tissue rest with vasoconstriction, calcium accumulation and dehydration.

Petersen and Levinson also called attention to another apparent inconsistency. The contraction of smooth muscle (which may represent the response either to sympathetic or parasympathetic stimulation) commonly has been regarded as tissue activity, but during the muscular contraction the capillaries are contracted, capillary permeability is diminished, metabolic processes are retarded and less energy is liberated. With relaxation, on the other hand, the vascular bed becomes dilated, capillary permeability is increased and metabolism is accelerated. The relaxation of smooth muscle, therefore, represents the parasympathetic status as defined above.

Inasmuch as the parasympathetic status and the sympathetic status represent states of tissue activity and tissue rest respectively, the same status obviously cannot obtain throughout the entire body at any given moment. This is well illustrated by the adaptive compensatory reactions between the peripheral and splanchnic blood vessels.

The stimuli which elicit widespread vasoconstriction at the periphery also elicit vasodilatation in the splanchnic area and *vice versa*. These changes are accompanied by corresponding changes in the permeability of the blood vessels and the distribution of leukocytes. The area in which the sympathetic status obtains exhibits leukopenia, that in which the parasympathetic status obtains exhibits leukocytosis. Leukopenia and leukocytosis, consequently, parallel compensatory vasoconstriction and vasodilatation and may be regarded as indices of the functional autonomic status in the respective areas.

The peripheral and splanchnic areas are so intimately interconnected through the autonomic regulatory mechanism that when extensive areas are involved, the slightest change in the autonomic status at the periphery gives rise to a corresponding change in the opposite direction in the splanchnic area, and *vice versa*, under both physiologic and pathologic conditions. Disease processes may result either in chronic fixation of an abnormal autonomic status or in increased instability of the autonomic nervous system, either of which conditions may result in inadequate compensatory reactions or overcompensation, giving rise to abnormal conditions of blood pressure (E. F. Muller, 1926).

In the light of our present knowledge of the innervation of the blood vessels (see Chapter VIII) the compensatory vascular reactions in the peripheral and splanchnic areas obviously cannot be explained on the basis of changes in sympathetic parasympathetic balance as commonly understood, but they can be explained on the basis of changes in the autonomic

status of these areas respectively. As previously stated, the peripheral blood vessels are not supplied with parasympathetic fibers. Neither has a parasympathetic innervation of the splanchnic vessels been demonstrated beyond question. The sympathetic nerves to the peripheral blood vessels, furthermore, include vasodilator fibers (see Chapter VIII). The peripheral vasomotor control, therefore, involves only the sympathetic nerves; consequently, an autonomic imbalance in the ordinary sense in this area is inconceivable. The control of the peripheral temperature-regulating mechanism, likewise, is effected mainly through the sympathetic nerves. Certain synergic reactions of organs which are innervated through both the sympathetic and parasympathetic divisions of the autonomic system, *e. g.*, coördinated reactions of the sphincter and detrusor muscles of the urinary bladder, also may be carried out in the absence of nerve impulses (Schilf, 1927). In the light of these observations, it must be clear that many visceral phenomena which have been regarded as manifestations of functional antagonism between the sympathetic and parasympathetic nerves must be explained on some other basis. In so far as they involve the functional activity of both sympathetic and parasympathetic nerves, these nerves are not mutually antagonistic, but synergistic.

In view of the data outlined above and our present knowledge of the humoral transmission of nerve impulses and the distribution of cholinergic and adrenergic fibers in both divisions of the autonomic nervous system, the concept of a clear cut functional difference between the parasympathetic and the sympathetic nerves is untenable. On the basis of this knowledge and the results of a study involving measurements, over an extended period, of 20 physiologic variables of which at least 12 are mediated at least in part through the autonomic nerves, in 62 children six to eleven years of age, and a factor analysis of these data, Wenger (1941) has proposed the following restatement of the theory of Eppinger and Hess:

(*a*) "The differential chemical reactivity and the physiological antagonism of the adrenergic and cholinergic branches of the autonomic nervous system permit of a situation in which the action of one branch may predominate over that of the other. This predominance, or autonomic imbalance, may be phasic or chronic, and may obtain for either the adrenergic or the cholinergic system. (*b*) Autonomic imbalance, when measured in an unselected population, will be distributed continuously about a central tendency which shall be defined as autonomic balance."

Factors Influencing the Autonomic Balance.—The Acid-base Balance.— The results of clinical studies reported by Hollo and Weiss (1925) have shown that calcium chloride administered intravenously in therapeutic doses reduces the bicarbonate content of the blood plasma but increases the H-ion concentration of the blood and the alveolar carbon dioxide tension. Calcium chloride and calcium lactate administered by mouth also reduce the bicarbonate content of the blood plasma. These results are in full agreement with those of Fürst (1925) and others, obtained in animal experiments, and show clearly that the acid-base balance can be changed in the direction of acidity by the administration of calcium and that an increase in the potassium-ion concentration results in a change in the acid-base balance in the direction of alkalinity.

Changes in the functional balance between the sympathetic and the parasympathetic nerves due to changes in the acid-base balance have been

amply demonstrated The results of experiments involving the stimulating effect of adrenin on the sympathetic nerves prove conclusively that the effect of adrenin is influenced by the chemical reaction of the fluids circulating through the organs in question In the experiments of Snyder and Andrews (1919), Snyder and Campbell (1920) and Snyder and Martin (1922), adrenin perfused through the portal system in turtles resulted in dilatation of the blood vessels when the H ion concentration of the perfusion fluid was low Certain experimental data cited by Balint also indicate a greater rise in blood pressure in response to a given dose of adrenin when the reaction of the blood is alkaline than when the acid base balance is shifted toward the acid side In some instances when the reaction of the blood tended toward the acid side, the administration of adrenin elicited no rise in blood pressure In perfusion experiments on the frog's heart Atzler and Müller observed inhibition, *i e* a parasympathetic reaction, when the perfusion fluid was acid and acceleration, *i e*, a sympathetic reaction when the perfusion fluid was alkaline

Weiss and Henkovics (1925) found that the effect of adrenin on blood pressure was reduced following the administration of calcium chloride which as stated above, shifts the acid base balance of the blood toward the acid side This result is in full accord with actual clinical findings Patients with hyperthyroidism commonly exhibit a shift in the acid base balance toward the alkaline side They also exhibit increased sympathetic reactivity to adrenin In general the degree of change toward the acid side corresponds to the degree of improvement The decrease in the reactivity of the sympathetic nerves to adrenin also corresponds to the reduction in the alkalinity of the blood (Csepai Hollo and Weiss 1925) Patients suffering with diseases which commonly are associated with hyperacidity, *e g* bronchial asthma diabetes insipidus etc likewise rarely if ever exhibit increased sympathetic reactivity to adrenin In many cases the reactivity of the sympathetic nerves to adrenin is actually subnormal (Balint 1927) Patients with diabetes mellitus exhibit a wide range of variation in the reactivity of the sympathetic system to adrenin In a study involving comparison of sympathetic reactivity and the acid base reaction of the blood in diabetic patients, Csepai, Hollo and Weiss (1925) found that sympathetic reactivity to adrenin was subnormal in those exhibiting hyperacidity, but increased in those who had been subjected to massive sodium bicarbonate treatment In certain cases in which they found subnormal sympathetic reactivity before treatment, adrenin elicited a normal or exaggerated response after alkaline therapy These results are in full accord with the results of animal experimentation cited above and strongly support the theory that sympathetic tonus is increased by a change in the acid base balance in the blood toward the alkaline side and parasympathetic tonus is increased by a change in the acid base balance toward the acid side

If such is the case, we should expect to find evidence of hyperacidity in all cases in which vagotonia as indicated by pharmacologic criteria exists The data bearing on this point as yet are meager but they afford evidence which is strongly suggestive Chronic gastric and duodenal ulcer almost invariably is associated with parasympathetic hyperirritability and hyperacidity (Lokin, 1925, Lande, 1926, Sunnitzky 1927, Balint 1927, and others) In certain cases of cholelithiasis, the dominant symptoms resemble

very closely those of gastric ulcer. This is true particularly of the reflex reactions of the stomach, including hypermotility and changes in gastric secretory activity which are manifestations of vagotonia. Although vagotonia usually is demonstrable in cases of cholelithiasis, the H-ion concentration of the blood falls within the normal range in many cases. In a clinical study of 14 patients with cholelithiasis, involving determination of the H-ion concentration of the blood and the elimination of alkali through the kidneys, Balint (1927) found that, although the H-ion concentration of the blood did not deviate beyond the normal limits in any of the 13 cases in which it was determined, the urine did not become alkaline or only slightly so following the injection of sodium bicarbonate in 9 cases, showed a neutral reaction in 1, and an alkaline reaction in the other 4. The majority of these cases (9 out of 14) exhibited alkali retention which, according to Balint, is associated with an acid condition of the tissues. It must be admitted, therefore, that the tissues were more acid than normal in these cases, although hyperacidity was not demonstrable in the blood. The results obtained in a limited number of cases of bronchial asthma, in general, corroborate the above findings in cases of cholelithiasis. On the basis of these findings, Balint concluded that some degree of hyperacidity is a common accompaniment of vagotonia, although the H-ion concentration of the blood may not deviate beyond the normal limits.

The Vasosensory Mechanisms.—Specific mechanisms of autonomic regulation such as the carotid sinus and the cardio-aortic and abdominal vasosensory mechanisms, described in Chapter VIII, play a significant rôle in the physiologic processes involved in the maintenance of the functional balance throughout the body. These mechanisms are involved particularly in the reflex control of circulatory and respiratory equilibrium which they exercise by maintaining and varying the tonic inhibition of the organs concerned in these essential life-maintaining functions and through the influence which they exert in the more general functions particularly of the sympathetic nerves.

In general the carotid sinus mechanism is activated by optimal conditions of oxygenation and blood pressure which favor bodily activity. In turn it tends to lower blood pressure to the level which is commensurate with the maintenance of its own activity. Conditions of low blood pressure, low oxygen tension or excess of carbon dioxide in the carotid sinus, on the other hand, tend to inactivate the carotid sinus mechanism, or reduce its inhibitory action, and release the restrained sympathetic mechanisms from tonic inhibition (Bielniski and Wierzuchowski, 1939). At the same time impulses emanating from the carotid sinus which elicit parasympathetic reflex activity are reduced. Like carotid sinus denervation, such conditions tend to produce hypertension and, in certain cases, hyperpnea (Heymans and Bouckaert, 1930; Winder, 1937, 1938). Under conditions of extremely low blood pressure, "paradoxical" reactions may result in no rise in blood pressure and respiratory failure.

The vasoreceptive mechanisms which normally exercise a regulatory inhibitory control over sympathetic activity, actually reducing the magnitude of vasomotor and other sympathetic reflex reactions to afferent nerve stimulation, also exercise a positive control through the parasympathetic nerves (Hering, 1927; Heymans, 1928; Bernthal and Motley, 1939), including increased intestinal tonus and motility (Tournade and Malmajac, 1929).

Adrenin in the circulating blood tends to sensitize the carotid sinus mechanism and thus increase its inhibitory effects both on blood pressure and respiration (Heymans, 1929). Data reported by Bettencourt (1935) and Chu and Hsu (1938) support the assumption that the adrenin actually increases the sensitivity of the carotid sinus mechanisms to the existing blood pressure; consequently, a depressor reaction may be produced independently of the peripheral depressor effects of adrenin. By increasing the inhibitory control of the carotid sinus mechanism over sympathetic reactions adrenin also exercises an inhibitory control over medulliadrenal secretion and thereby provides homeostatic limitation on its own account. In like manner, adrenin may limit other sympathetic responses (Darrow and Gellhorn, 1939, Gellhorn, Darrow and Yesinick, 1939).

The action of acetylcholine in the carotid sinus, according to Heymans *et al* (1935), may result in hypertension by decreasing sympathetic inhibition. This undoubtedly is due to cholinergic inactivation of the carotid sinus mechanism, since the effects are similar in kind to those of carotid sinus denervation. The physostigmine-like action of ergotamine in the carotid sinus which, according to Bacq, Brouha and Heymans (1932), may result in hypertension also indicates failure of sympathetic inhibition due to depression of the carotid sinus reflexes (Heymans, Regniers and Bouckaert, 1930). The increased blood pressure in human subjects following the administration of ergotamine, as reported by Freeman and Carmichael (1936), probably can be explained most satisfactorily on the same basis.

Carotid sinus dysfunction not uncommonly is manifested in syncopal attacks, probably due to hyperirritability of the carotid sinus mechanisms (Weiss and Baker, 1933). Ferris, Capps and Weiss (1935) have classified such attacks as (1) cerebral, (2) cardiac and (3) vasomotor, depending upon which of the carotid sinus mechanisms are most involved. In the cerebral attacks the reflexes initiated in the carotid sinus affect primarily the brain or cerebral circulation. In the other types, the embarrassment of the general circulation secondarily results in syncope. In these latter cases convulsions may occur not as a direct effect of carotid sinus hyperirritability but in consequence of the syncopal attack (Friedberg and Sloan, 1937). In idiopathic epilepsy, as observed by Weiss and Baker (1933), carotid sinus pressure does not cause seizures. Epilepsy, as shown by Marinesco and Kreindler (1931), may actually be associated with carotid sinus hyposensitivity, in which case seizures may result from failure of the carotid sinus mechanism to protect the brain from mechanical shocks transmitted through the circulation. Darrow (1943) admitted this possibility but on the basis of electroencephalographic evidence advanced the opinion that lack of hydrodynamic control is less important in the etiology of epilepsy than inadequate buffering of the autonomic discharges to the brain.

Hypersensitivity and overregulation by the carotid sinus mechanisms are indicated in certain cases of schizophrenia by the depression of sympathetic functions (Gellhorn, 1938, Darrow and Solomon, 1939, 1940). The blood pressure tends to be low (Freeman, Hoskins and Sleeper, 1932) and the pulse slow (Hoskins and Walsh, 1932). Emotional hypoglycemia is the rule (Bowman and Kasanin, 1929, Whitehorn, 1934, Gildea, Mailhouse and Morris, 1935) probably due to increased vago-insulin secretory activity (Gellhorn, Feldman and Allen, 1941). The observation reported by Lindeman (1935) that schizophrenic symptoms are aggravated by the

subcutaneous injection of adrenin supports the assumption that in resistant, uncoöperative patients the carotid sinus may become sensitized by increased production of adrenin (Darrow and Solomon, 1940). The effectiveness as a therapeutic agent in schizophrenia of ergotamine, a drug which desensitizes the carotid sinus, also supports this point of view (Baber and Tietz, 1937).

Tests of Autonomic Functional Balance.—A test of autonomic function can be significant only if it circumvents the mutually antagonistic actions of the sympathetic and parasympathetic nerves so that it may indicate clearly whether an observed reaction is due to increased activity in one division of the autonomic system or to decreased activity in the other. Tests which merely indicate a functional imbalance are of little value and may even be misleading, since they do not define the reactions in question in the neural and neurohumoral systems. Autonomic reactions, furthermore, may bear one relationship to the initiating processes in the nervous system under certain conditions and another relationship under other conditions.

Circumvention of the difficulties in interpreting observed autonomic reactions in terms of neurohumoral processes have been attempted in various ways: (1) by recording the reactions of mechanisms which are innervated through only one division of the autonomic system, *e. g.*, the nictitating membranes; (2) by elimination of either the sympathetic or the parasympathetic innervation of the organ in question; (3) by assaying in vivo or in vitro the neurohumoral mediator liberated; (4) by analysis of the reactions to appropriate pharmacologic agents; (5) by recording the action potentials of the respective autonomic nerves. All of these methods have been found useful but the interpretation of the results obtained is beset with difficulties due to homeostasis, since autonomic reactions tend not only to bring about adaptive changes but also to maintain the constancy of the internal milieu. The criteria by which the sympathetic or parasympathetic character of a given mechanism may be determined, furthermore, are varied and not always consistent with one another.

Tests Based on Singly Innervated Structures.—The nictitating membrane receives its efferent innervation solely through adrenergic sympathetic fibers; consequently, it provides an ideal sympathetic indicator. It has been utilized as such by various investigators, including Brown (1934), Rosenblueth and Schwartz (1935) and Gellhorn and Darrow (1939). It provides an index not only of sympathetic excitation but also of inhibition of sympathetic tonus. Its reaction to adrenin may be enhanced by eserin and decreased by atropine (Rosenblueth, 1932; Secker, 1937). It may react to large doses of acetylcholine in animals in which it has become sensitized following denervation (Morrison and Acheson, 1938). These properties, as Darrow (1940) pointed out, do not seriously detract from its usefulness as a sympathetic indicator under normal conditions.

The sweat glands are innervated solely through cholinergic sympathetic fibers. The secretory activity of these glands has been utilized extensively as an index of sympathetic activity. Sweating and the concomitant changes in the electrical resistance of the skin, particularly in the palms of the hands, are extremely sensitive to changes in the level of activity of the sympathetic nerves. Excessive spontaneous sweating probably always indicates exaggerated sympathetic reactivity.

The adrenal medulla derives its efferent innervation solely through sympathetic preganglionic fibers. Since the secretory product of the gland is a sympathomimetic hormone the production of which depends on sympathetic excitation, it may be utilized as a sympathetic indicator. The response to adrenin, as indicated particularly by the magnitude of the rise in blood pressure produced by a given dosage, provides a fairly reliable index of the level of sympathetic reactivity.

Tests Based on Sympathetic or Parasympathetic Denervation.—This method has been widely utilized in the delimitation of responses of mechanisms innervated through both divisions of the autonomic system. It should be limited to acute experiments since the denervated tissues may become sensitized to the humoral agent whose neural counterpart has undergone degeneration. In the case of certain mechanisms, *e.g.*, the pupil as observed by Darrow and Gellhorn (1939), a degree of sensitization may occur even during the period of an acute experiment.

The pupil provides a convenient mechanism for the application of this method since the sympathetic nerves to one eye may be severed without affecting the innervation of the other eye which affords a convenient experimental control. The difference between the reactions of the sympathetically denervated pupil and the normally innervated one on the opposite side provides an index of the concomitant sympathetic activity. Section of the oculomotor nerve likewise results in parasympathetic denervation of the pupil leaving its sympathetic innervation intact. The results of this experimental procedure show clearly that dilatation of the pupil in response to painful stimulation is due to inhibition of parasympathetic tonus to a greater extent than to sympathetic excitation (Darrow 1910). Sympathetic excitation undoubtedly contributes to the pupillary response to emotional stimulation (Carlson, Gellhorn and Darrow 1941; Hodes and Magoun 1911) and probably also when the inhibitory effects of adrenin have been eliminated (Darrow and Gellhorn 1939). The knowledge that parasympathetic inhibition may play a major role in a response which has commonly been regarded as indicating sympathetic activity suggests the desirability of a reexamination of the evidence on which similar interpretations have been based in the case of other mechanisms with dual autonomic innervation.

The salivary glands, particularly the parotid, provide a useful indicator particularly for parasympathetic reactivity. Data reported by Lourie (1943) support the assumption that the rate of parotid gland secretion is not influenced by sympathetic nerve impulses; consequently, elimination of its sympathetic innervation is unnecessary. Lourie has described a convenient technic for recovery of the parotid secretory output in children and determination of the rate of secretion. His findings support the assumption that children are essentially parasympatheticotonic with respect to the parotid gland and become less so as they approach puberty.

Blood pressure provides a useful indication of autonomic activity only when it is interpreted critically. A rise in blood pressure frequently indicates increased sympathetic activity, but an equal rise may actually be due to a decrease in parasympathetic tonus. A fall in blood pressure likewise may be due to inhibition of sympathetic tonus. The prevailing lack of correspondence between changes in blood pressure and changes in valid sympathetic indicators such as the nictitating membrane has been empha-

sized by the results of various studies, particularly those of Rosenblueth and Schwartz (1935) and Watkins (1938) Vasomotor inhibition particularly by impulses emanating from the carotid sinus is an important factor in blood pressure, as indicated by the hypertension following carotid sinus denervation (Heymans and Bouckaert, 1931, 1935), which may be prevented by prior complete sympathectomy (Heymans and Bouckaert, 1935, Grimson, 1939).

Vasomotor tonus may be utilized as an indicator of autonomic function in a wide variety of conditions but identification of vasoconstriction with sympathetic activity is not a rational procedure, since the sympathetic innervation of most of the blood vessels includes both vasoconstrictor and vasodilator fibers Sympathetic vasodilatation has long been recognized in the skeletal musculature, where obviously it may serve an emergency function This is particularly marked in "animals of the chase" such as the dog and the hare (Burn, 1938). In most mammals, including man, the cutaneous and the splanchnic vessels are supplied with adrenergic vasoconstrictor and cholinergic vasodilator fibers

Tests for the reactivity of the adrenergic and the cholinergic systems are helpful particularly in the diagnosis and treatment of peripheral vascular diseases and other neurocirculatory disorders. Among those which have been used particularly to determine the capacity of the patient for vasodilatation may be mentioned induced fever (Brown, 1926, Adson and Brown, 1929, Adson, 1936), spinal and general anesthesia (Scott and Morton, 1930), nerve block (White, 1930, Scott and Morton, 1931), warming of the extremities (Landis and Gibbon, 1933) and the administration of cholinergic drugs Tests of sympathetic reactivity which may be used in the diagnosis of hypertension include the cold pressor test (Hines and Brown, 1933, White and Gildea, 1937), skin temperature determinations (Craig, Harton and Sheard, 1933), plethysmographic blood volume and blood flow determinations and photoelectric plethysmographic technics (Hertzman and Dillon, 1938, 1940)

Assay of the Output of Humoral Mediators.—The assay of the humoral mediators may be accomplished in vivo in the same animal or a second one by registration of their effects on denervated sensitized organs, or in vitro either by their effects on strips of excised, sensitized tissue or by chemical tests. The two kinds of sympathin, E and I, correspond in their effects to those of an undifferentiated adrenin and to those of a partially oxidized adrenin, "nor adrenin," which has been deprived of its inhibitory action (Bacq, 1934, 1935). It is significant, furthermore, that the inhibitory action of sympathin I or of inhibitory adrenin is apparent only in tissues which have a parasympathetic (cholinergic) nerve supply and in those which have no parasympathetic nerves but are supplied with cholinergic sympathetic fibers, the effector endings of which, or the effectors themselves, are sensitive to parasympathomimetic drugs An inhibitory action of adrenin on purely adrenergic effectors, except secondarily through the effects of adrenin on the cholinergic sympathetic ganglia (Marazzi, 1939) or through the carotid sinus and other moderator nerves (Heymans, 1929, Gellhorn, Darrow and Yesinick, 1939, Bronk, Pitts and Larrabee, 1940), has not been demonstrated beyond question.

The nictitating membrane sensitized by denervation is a relatively pure adrenergically excitable structure; consequently, it provides a sensitive

indicator of excitatory (E) sympathin (Liu and Rosenblueth, 1935, Simeone, 1937) Inhibitory (I) sympathin or inhibitory adrenin exerts little effect on it or none at all The chronically denervated nictitating membrane has been used extensively for the in vivo assay of sympathin E and adrenin (Cattell, Wolff and Clark 1934, Partington 1936, Bender and Siegel, 1940) The early differentiation of excitatory (E) from inhibitory (I) sympathin was based mainly on studies of the differential reactions of the nictitating membrane and the non-pregnant uterus of the cat As observed by Cannon and Rosenblueth (1933), the excitatory sympathin liberated by stimulation of the hepatic nerves was sufficient to cause contraction of the nictitating membrane but had little inhibitory effect on the non-pregnant cat's uterus, whereas inhibitory sympathin liberated by stimulation of the sympathetic nerves of the stomach and intestine cause marked relaxation of the uterus but relatively little contraction of the nictitating membrane Cannon and Rosenblueth (1935) showed further that an amount of sympathin E sufficient to produce a measured contraction of the nictitating membrane produces but slight dilatation of the pupil After parasympathetic denervation of the iris the same amount of sympathin E caused appreciable pupillary dilatation, consequently they inferred that sympathin E must in some manner stimulate the cholinergic constrictor mechanism Sympathin I or inhibitory adrenin on the other hand, relaxes the cholinergic constrictor mechanism, thus facilitating dilatation (Yonkman, 1930) These data support the assumption that sympathin E and sympathin I may work synergistically by causing contraction of the dilator muscles and simultaneous relaxation of the constrictor and thus produce greater dilatation of the pupil than would result from excitation alone The operation of the humoral mediators, sympathin E and sympathin I, on the pupil obviously parallels the effects of nerve stimulation where sympathetic excitation and parasympathetic inhibition may result in synergistic action The completely denervated iris in the eserinized animal provides a useful indicator of the synergistic effects of excitatory and inhibitory adrenin It has also been utilized by Bender and Weinstein (1940) as an adrenergic indicator, with the denervated facial musculature as a cholinergic indicator

The musculature of the gastro-intestinal tract, particularly that of the large intestine, has proved useful as an indicator of the inhibitory action of sympathin and adrenin Since gastro-intestinal motility and tonus are maintained through cholinergic parasympathetic nerves this musculature may also be used as an indicator of cholinergic activity (Loew and Patterson, 1935, Youmans and Meek 1937) The observation that the inhibitory effects of nerve stimulation may be abolished by splanchnicotomy and restored by adrenin supports the assumption that they are mediated through the sympathetic nerves Youmans Meek and Herrin (1938) employed both innervated and denervated Thiery fistulæ in the same dog for simultaneously testing the effects of nerve stimulation and those of humoral agents

The rate of the denervated heart provides a useful indicator for the effects of humoral agents and has been utilized extensively (Cannon and Uridil, 1921, Cannon, Lewis and Britton 1926, Newton, Zwemer and Cannon, 1931, Rosenblueth and Phillips 1932, Whitelaw and Snyder, 1934) It is sensitive to both adrenergic and cholinergic mediators but the cho-

linergic effects may be regarded as negligible except in the presence of eserine or similar drugs. In any case, the excitatory and inhibitory actions of sympathin or adrenin are synergistic.

Tests Involving Reactions to Pharmacologic Agents.—On the basis of actual experience, various investigators have maintained that the existence of an autonomic imbalance and its character can be determined by pharmacodynamic methods. Others have denied this possibility on the basis of data which indicate that certain individuals react strongly to both sympathetic and parasympathetic stimulants and the conflicting results obtained in many pharmacodynamic studies. In general, individuals with exaggerated sympathetic tonus react more strongly to sympathomimetic agents than those with normal autonomic balance. Individuals with exaggerated parasympathetic tonus, likewise, react more strongly to parasympathomimetic agents than those with normal balance. The effect of a given dose of a drug like ergotamine, which tends to block the sympathetic or adrenergic nerves, or atropine, which tends to block the parasympathetic or cholinergic nerves, therefore, varies according to the functional balance of the autonomic system. In the presence of exaggerated sympathetic tonus a larger dose of ergotamine is required to block adrenergic function than in the presence of normal autonomic balance. Likewise, in the presence of exaggerated parasympathetic tonus a larger dose of atropine is required to block cholinergic function than in the presence of normal autonomic balance.

The assumption that ergotamine merely tends to block adrenergic conduction is misleading. Its primary action on smooth muscle, particularly that which is cholinergically activated, like the gastro-intestinal muscle, is to cause contraction (Rothlin, 1929). In the intact animal it increases intestinal motility, causes extreme miosis (Dale, 1906; Crouch and Thompson, 1939), lowers blood sugar (Shpiner, 1929) and decreases blood pressure (Wright, 1930). In certain cases the administration of this drug may be followed by increased blood pressure probably due to the contraction of muscular organs. Desensitization of the carotid sinus by ergotamine (Heymans *et al.*, 1930) may be a contributing factor in the rise in blood pressure in these cases. Ergotamine blocks the inhibitory effect of adrenin or sympathetic stimulation on cholinergically activated mechanisms. The inability of adrenin or sympathetic stimulation to block the spontaneous activity or relax the tonus of intestinal muscle in the presence of ergotamine can be explained most satisfactorily on this basis (Darrow, 1943). In the human placenta, which is devoid of nerves but rich in choline (Chang and Gaddum, 1935), constriction of the blood vessels by adrenin is blocked by ergotoxine (Euler, 1938). Cholinergic vasodilatation probably is normally inhibited by adrenergic sympathetic stimulation or inhibitory adrenin, resulting in constriction which is synergic with adrenergic constrictor activity. This inhibition of the vasodilators does not take place following the administration of ergotoxine: consequently, the rise is less marked or there may be an actual fall in blood pressure. A similar vasomotor reversal after eserine, which is abolished by atropine, has been demonstrated (Bülbring and Burn, 1935; Herwick *et al.*, 1939). This also suggests that the inhibitory effects of adrenergic stimulation may be blocked in the presence of sufficient acetylcholine. Linegar *et al.* (1939) have shown that the depressor effects of acetylcholine may be potentiated by er tamine

and that this action may be reversed by atropine. The chief value of ergotamine as an indicator of autonomic function undoubtedly lies in its effectiveness in testing for the presence of sympathetic inhibitory and adrenin inhibitory effects on cholinergic functions.

The use of atropine to determine the role of cholinergic mechanisms in a given response has become almost routine in physiologic experiments. The measurements sought by its use have been mainly of two types: (1) an index of the normal cholinergic activity as indicated by the changes induced when that activity is blocked, and (2) an index of sympathetic function as indicated by the total residual activity following blocking of the cholinergic mechanisms. The possible effects of the drug on cholinergic transmission of nerve impulses in the sympathetic ganglia, the adrenal medulla and the central nervous system and the possible compensatory action of the carotid sinus and other moderator nerves may vitiate both these effects to some extent (Darrow, 1943). Atropine has nevertheless been found useful in the study of autonomic functions particularly in psychopathic patients (Lentress and Solomon, 1936) and synergic and antagonistic pharmacologic responses in normal and diseased human subjects (Myerson, Loman and Dameshek, 1937, Brokoff and Kaldenberg, 1938).

Autonomic Action Potentials.—Electric recording of the activity of autonomic effectors has been utilized widely in studies of autonomic activity. The literature bearing on the use of action potential records in investigations of various aspects of the physiology of the autonomic nerves is too extensive to be reviewed in this connection. Analytic studies of the electric responses in smooth muscles in various organs such as the nictitating membranes, pilo-erectors, intestine, uterus, urinary bladder and ureters and their autonomic nerves carried out by various investigators including Rosenblueth, Leese and Lambert (1933), Lambert and Rosenblueth (1935), and Bozler (1938) indicate that the action potential records obtained in inhibitory responses differ from those obtained in excitatory responses. With respect to the salivary glands the action potential records obtained during sympathetic stimulation differ from those obtained during parasympathetic stimulation (Bronk and Gesell, 1926).

Adrenin, atropine and certain other pharmacologic agents, as indicated by action potential records (Marazzi, 1939), exert a damping influence on cholinergic transmission in autonomic ganglia, whereas such transmission is facilitated by parasympathomimetic drugs. Action potential records have been employed in investigations involving problems of autonomic control particularly by Hinsey and Gasser (1930) and Bishop, Heinbecker and O'Leary (1934), and in studies carried out to determine the specific functional relationship of the carotid sinus nerves to sympathetic regulation by Bronk (1931), Bronk and Stella (1932, 1935), Fischer and Lowenbach (1934), Bonge and Stella (1934, 1935), Samaan and Stella (1935) and Pitts (1942). Electrical recording technics undoubtedly can be employed still more widely in studies involving the synergic and antagonistic actions of adrenergic and cholinergic autonomic mechanisms.

CHAPTER XXI

THE AUTONOMIC NERVOUS SYSTEM IN DISEASE

Clinical Significance of Autonomic Dysfunction.—The data outlined in chapter XVIII show clearly that disease processes not uncommonly are accompanied by histopathologic lesions of autonomic ganglia and ganglion cells or central autonomic centers. Such lesions usually are non-specific. In some instances they are obviously related to a disease process: in others a direct relationship of the autonomic lesions to a disease process is not apparent. The data available in any given case usually do not indicate whether the histopathologic alterations observed antedated the onset of the disease with which they are associated or arose as a result of the disease process. In either case they may play a rôle in the progress of the disease and its sequelæ. The autonomic nerves, furthermore, may play significant rôles in disease processes in the absence of recognizable neural lesions, due to modified reflex activity or increased or decreased stimulation, inhibition or depression of central autonomic centers.

Lesions of the autonomic ganglia and ganglion cells which arise during the courses of certain diseases affect their progress due to their stimulating or depressing effects on the vasomotor nerves, the visceral muscles and glands. Vasomotor depression results in a fall in blood pressure and changes in the distribution of the blood in the organs. The volume of blood in the splanchnic area is greatly increased, while other parts of the body, including the central nervous system, the skin and the skeletal muscles are relatively ischemic. Infectious diseases in children not infrequently are accompanied by sympathetic hyperexcitability. Severe acute intoxication in children may be accompanied by sympathetic hypotonus which always indicates an unfavorable prognosis. The toxic effects of disease on the autonomic ganglion cells and the central autonomic centers result in modification of various visceral functions. Depression of the sympathetic or stimulation of the parasympathetic nerves results in gastro-intestinal hypermotility, retardation of the cardiac rhythm, etc. On the contrary, stimulation of the sympathetic or depression of the parasympathetic nerves results in constipation, cardiac acceleration, etc. Stimulation or depression of the secretory nerves due to the toxic effects of disease, likewise, may result in far-reaching glandular dysfunction. Reflex vasoconstriction initiated and maintained by the stimulating effects of peripheral lesions, *e. g.*, arthritis, not only retards recovery, due to limitation of the blood supply to the part in question, but also constitutes a causative factor in the production of pain. Modification of the autonomic status, due to the toxic effects of disease, not infrequently results in disturbances in metabolism due to changes in the permeability of the capillaries and the tissue elements and shifts in the acid-base balance.

Certain individuals exhibit excessive autonomic lability and an inability to achieve rapidly certain necessary autonomic adjustments, due to inherited constitutional factors. In these individuals, particular functional disabilities which form the focal points for certain diseases, such as mi-

graine, urticaria, colitis, goiter, glaucoma, etc., not infrequently are precipitated by environmental changes to which the autonomic adjustment has been inadequate. More frequently the symptomatology is indefinite, involving vague pains and discomfort which may be referred to various organs: nausea, headache, respiratory distress, etc., in the absence of recognizable causative factors. These individuals range from organic well-being through periods in which organic discomfort is perceived subjectively to the acute episodes which the physician recognizes as clinically definable and objectively demonstrable disease, although he is able to recognize no causative factor other than autonomic disintegration. In the presence of organic disease this autonomic lability is manifested particularly in the vascular and glandular reactions to the stimulating or depressing effects of toxins and other irritating factors, resulting in far reaching disturbances, particularly in tissue nutrition and endocrine balance, with unfavorable effects on the progress of the disease. Emotional behavior, as outlined in Chapter IV, is mediated at least in part through the hypothalamic centers which are involved in the higher integration of autonomic reactions. The visceral components of emotional expression represent the responses of the organs in question to the discharge of impulses from these centers via both the sympathetic and parasympathetic nerves. Hypothalamic integration also plays a significant rôle in emotional states associated with hypothalamic lesions, which include alternating moods of excitement and depression with associated alterations in visceral functions.

The most primitive components of emotional behavior spring from the vital requirements of the organism. The higher forms of emotional experience undoubtedly are derived from the same sources and never become entirely independent of their primitive prototypes. Autonomic reactions, therefore, play a part both in sensory experiences and emotional expression. The autonomic system thus exerts a significant influence in the dynamics of the psychic life (von Wyss, 1937).

The hypothalamic neural mechanisms, like other subcortical ones, are subject to inhibitory influences emanating from the cerebral cortex but are capable of independent activity in conformity with certain definite reaction patterns. Such activity in the hypothalamus and the thalamus plays an important role in the involuntary control of both somatic and visceral functions, such as bodily posture, facial expression, gastro-intestinal tonus, etc. During emotional stress the subcortical mechanisms involved are relatively free from cortical control, consequently, their influence in both somatic and visceral functions is exaggerated. In the somatic realm this results in the postures and facial expressions characteristic of the various emotions. In the visceral realm it results in functional disturbances in varying degrees, depending in a large measure on the nervous constitution of the individual. Although specific visceral reactions probably are not usually directly correlated with specific psychic or emotional states (Denning, Fischer and Beringer, 1930), the visceral disturbances, under normal conditions, constitute an essential part of the emotional picture but in many instances they become exaggerated to the point of positive visceral disorders.

The individual with a stable and well-disciplined nervous system is able to suppress the outward expressions of emotion in a high degree. His visceral responses to emotional excitation may be intense momentarily

but they usually do not result in serious visceral disorders. Persistent disorders of visceral functions due to emotional disturbances occur most commonly in association with psychic or nervous instability. They are none the less real and, since they are mediated through the autonomic nervous system, they are not subject to direct voluntary control and persist as long as the autonomic hyperstimulation prevails. Treatment of the visceral symptoms without reference to the emotional cause, therefore, must be regarded as futile. On the other hand, if the patient can be restored to emotional equilibrium, the visceral disorders of emotional origin soon subside.

Endocrine Disorders.—Chronic Adrenal Insufficiency (Addison's Disease).—Chronic adrenal insufficiency, first described by Addison in 1855, is a relatively rare disease which usually develops in the third or fourth decade of life. It is characterized by adynamia, gastro-intestinal disturbances (constipation alternating with diarrhea), pigmentation of the skin and mucous membranes and low blood pressure. Body temperature is often subnormal, particularly in the later stages of the disease.

Tuberculosis involving the adrenal glands has been found to be the most common cause of this disease. Simple atrophy, chronic interstitial inflammation resulting in atrophy, and malignant disease invading the adrenal capsules or restricting their blood supply due to pressure also have been recognized as causes of adrenal insufficiency. In a certain number of cases, the adrenal glands show no lesion but adrenal hypofunction is brought about by pressure, inflammation or degenerative changes involving the celiac ganglia.

While the symptom-complex associated with adrenal insufficiency rests on a subnormal output of adrenin, some of the dominant manifestations of the disease, *e. g.*, the gastro-intestinal disorders and low blood pressure, are directly referable to a functional autonomic imbalance. Not infrequently the dominant symptoms indicate general depression of the sympathetic nerves.

Degenerative lesions involving the adrenals result not only in diminution of the functional tissue but also in impairment of the secretory function of the nerve fibers supplying these glands; consequently, the remaining secretory tissue is deprived of its normal stimuli. Diminution of the adrenin output in turn results in lowered sympathetic tonus. The low blood pressure, subnormal body temperature and asthenia associated with adrenal hypofunction are symptoms of sympathetic hypotonus.

Certain of the older investigators attempted to explain the excessive pigmentation of the skin, which occurs as an inconstant symptom of adrenal insufficiency, on the basis of disturbed autonomic function. Most of the data available do not support this theory. On the basis of a critical study of the anatomy and physiology of the pigmented portions of the skin, Bory (1926) advanced the opinion that the basal cells of the stratum germinativum act in close correlation with the adrenals and that, under certain physiologic conditions, the skin either produces adrenin or stimulates the adrenals to secrete. He regarded the excessive pigmentation of the skin, in adrenal insufficiency, as the result of overproduction of melanin by the skin in its attempt to compensate for adrenal hypofunction. The implied correlation between the skin and adrenals probably is brought about, at least in part, through the autonomic nerves.

in small doses increases liver autolysis, presumably due to increased cell permeability. Dresel (1929), furthermore, advanced experimental data on the basis of which he concluded that the active agent circulating in the blood of patients with exophthalmic goiter is far more active than any known thyroid preparation. Aub and his associates (1929) also have shown that the increased tissue permeability and associated increased metabolic activity in exophthalmic goiter patients result in a negative calcium balance. All these findings strongly suggest the existence of a parasympathetic status as defined by Petersen and Levinson (Chapter XX).

The dominant symptoms of hyperthyroidism, including tachycardia, exophthalmos, dilated pupils, perspiration and diminished gastric secretion, indicate sympathetic overstimulation. The autonomic nervous system, consequently, plays an important role not only in the underlying physiologic state of the body but also in the symptom-complex associated with hyperthyroidism. The nervous factors undoubtedly merit greater consideration in the treatment of this disease than usually has been accorded them since the autonomic dysfunction associated with the disease in turn affects the thyroid gland unfavorably. Measures which tend to restore the autonomic functional balance, therefore, tend to remove one of the chief sources of irritation of the thyroid gland.

Parathyroid Disease.—Vassale and Generali (1900) first called attention to a relationship between parathyroid extirpation and the symptoms of tetany which follow the removal of these glands in certain animals. Parathyroidectomy also gives rise to symptoms of tetany in man. Transplantation of parathyroids or injection of parathyroid extract ameliorates the symptoms and sometimes cures tetany. The metabolic disturbances following parathyroidectomy strongly suggest that the parathyroid hormone exerts an influence on the autonomic nervous system. According to certain investigators it exerts an inhibitory influence on the sympathetic nerves and adrenals. Parathyroid tetany may be aborted in certain cases by extirpation of the adrenals. On the other hand, active symptoms may be brought on by injection of adrenin in cases of latent tetany. The parathyroids also sustain an important functional relationship to the gonads. Parathyroidectomy is not followed by tetany in castrated animals. Subsidence of the symptoms of tetany in parathyroidectomized animals, following castration, furthermore, has been reported. The administration of parathyroid extract produces a fall in blood pressure in normal animals. Excessive or prolonged administration of this extract produces a very high calcium and phosphorus content in the blood serum and eventually results in convulsions and death.

The mechanism of parathyroid tetany is not fully known. On the basis of an experimental investigation carried out on dogs, West (1935) advanced the opinion that a circulatory factor acting peripherally upon some site in the muscles causes repeated contractions of individual muscle fibers and electric hyperexcitability. He also demonstrated the necessity of intact spinal reflex arcs for the conversion of essential or fibrillary tetany into its elaborate clonic and tonic forms and the independence of these forms of tetany of impulses emanating from central nervous centers higher than the spinal cord.

Hypophyseal Disorders.—The hypophysis is a complex gland which produces multiple hormones and subserves a variety of functions, some of

which have no obvious relation to the autonomic nerves. The posterior lobe is innervated mainly through the hypothalamico-hypophyseal tract The anterior lobe receives some fibers from this tract but is innervated mainly through sympathetic fibers derived from the cavernous plexus Some of the functions of the hypophysis undoubtedly are influenced by nerve impulses but much of its secretory activity is regulated through hormonal agents quite independently of the autonomic nerves (see Chapter XVI)

In view of the numerous hormones produced in the hypophysis and its complex interrelationships with other endocrine glands, including the gonads, hypophyseal dysfunction is expressed in a wide variety of disorders, including abnormal growth and sexual development, disturbances in carbohydrate and water metabolism, thyroid and adrenal dysfunction, adiposity, somnolence, etc

Many investigators, particularly those of the French school headed by Camus and Roussy, have supported the theory that many of the disorders which have been attributed to hypophyseal dysfunction, such as changes in the osseous system, adiposity, diabetes insipidus, etc., even though associated with lesions of the hypophysis, are caused by hypothalamic lesions This theory is supported, for certain disorders associated with hypophyseal lesions, by the results of extensive experimental studies, outlined in Chapter IV, of the effects of experimental lesions definitely localized in various parts of the hypothalamus.

The relief of disorders such as polyuria and obesity, in certain cases, by the administration of the appropriate hypophyseal hormones does not prove the independence of the hypophyseal dysfunction of a causative lesion in the hypothalamus On the other hand, the results of certain experiments, particularly those reported by Smith and Engle (1927), in which transplantations of anterior hypophyseal tissue in immature mice and rats rapidly induced precocious sexual maturity strongly suggest that sexual precocity may result from hypophyseal dysfunction which is not necessarily related to a neural cause Transplantation of anterior hypophyseal tissue in sexually mature animals also elicited marked reactions in the gonads and other genital organs.

In the experiments of Smith and Engle, the direct influence of hypophyseal hormones on the gonads and through them on the other genital organs was demonstrated also by the effectiveness of anterior hypophyseal transplants in castrated female and male animals. The effects of such transplants were not diminished by extirpation of the thyroid or adrenal glands Transplantations of endocrine gland tissue other than that of the anterior hypophyseal lobe neither retarded nor accelerated the development of the immature genital organs.

Hypophyseal tumors may give rise to diverse disorders Some of these can be accounted for most satisfactorily on the basis of increased hormone production due to hyperplasia of certain constituents of the gland Others obviously are due to the effects of pressure exerted by the tumor mass on adjacent neural structures, particularly the hypothalamus, or functional interruption of the hypothalamico-hypophyseal tract.

Disorders Referable to the Ovaries.—Our knowledge regarding the relation of the ovarian hormone to the autonomic nervous system has been greatly advanced during recent years, particularly by the results of studies in

to preoperative routine, and (3) patients with hyperthyroidism who had not received iodine therapy, Segal, Binswanger and Strouse (1928) observed no marked change in the metabolic rate on the day of operation in the first two groups but a marked rise in the third group on the morning of the expected operation

The effect of the emotions on the digestive functions is most striking Cannon (1911) described instances of complete inhibition not only of gastro-intestinal motility but also of the secretory activity of the digestive glands in consequence of emotional stress Mental work without excitement according to Delhougne (1926), does not influence gastric secretion Miller, Bergeim and Hawk (1920), however, reported marked disturbances of gastric secretion in students due to anxiety over examinations Persistent worry not infrequently results in indigestion Fear may inhibit salivary gastric and pancreatic secretion The entire digestive process likewise, may be profoundly disturbed by anxiety or distress On the basis of a study of the psychic and emotional factors in disorders of the digestive tract McLester (1927) estimated that one-third of the patients with digestive disorders have no recognizable organic disease but are suffering because of lack of emotional balance

Instances of digestive disorders due to emotional stress could be multiplied indefinitely Emotional excitement does not result in comparable digestive disorders in all persons The gastro-intestinal reaction to an emotion in a large measure, depends on the functional condition of the autonomic nervous system, the endocrine glands and the acid base balance According to Lueders (1928), "the gastro-intestinal reaction to an emotion persists only as long as the original object causing the emotion is present In other words, the visceral expression of an emotion ceases when the emotion is changed to an abnormal syndrome or mood" The normal autonomic nervous system tends to maintain normal gastro-intestinal function even though a dominant emotionalism has become habitual following the removal of the cause of the emotional reaction According to Lueders, many patients with psychoses exhibit normal or increased gastro-intestinal function He usually found no depression of gastro-intestinal motility or secretory activity in psychoses except when associated with somatic disorders or when the patient exhibited autonomic dysfunction According to his findings, gastro-intestinal function is increased in psychotic patients of the vagotonic type

In a roentgen-ray study of gastric motility during emotional excitement, Todd and Rowlands (1930) described characteristic patterns of gastric activity which are correlated with the external manifestations of autonomic stimulation When these external manifestations were suppressed, the pattern of gastric activity became markedly changed After a period of training, certain definite gastric responses could be evoked by appropriate psychic stimulation

In most cases of impaired digestion due to emotional excitement, the symptoms referable to the digestive organs are caused by inhibition of gastro-intestinal motility and secretion of the gastric juices due to sympathetic stimulation According to Stokes and Pillsbury (1930), emotions in general and depressant or unpleasant emotions in particular exert chiefly an inhibitory effect both on gastro-intestinal motility and secretory activity Gastro-intestinal hyperactivity due to emotional stress, though

not unknown, is less common and, in most cases, less persistent In these cases, the symptoms may be caused either by sympathetic inhibition or parasympathetic stimulation

Mucous colitis probably is invariably associated with sacral parasympathetic hyperstimulation. Certain physiologic and pathologic conditions may be regarded as predisposing factors, but the most common cause of this disorder is emotional tension. The three emotions with which mucous colitis is most commonly associated, according to White, Cobb and Jones (1939), are anxiety, guilt and resentment. Preoccupation with personal problems tends to prolong emotional tension and, consequently, the parasympathetic stimulation, leading to a chronic state of colonic irritation.

Gastro-intestinal neuroses, according to Menninger (1937), are primarily emotional They can be adequately treated only as the dynamic aspects of the personality of the patient are understood Therapy directed toward the stomach or intestine usually is ineffective. Rational therapy in these cases must be directed toward the total personality of the patient.

The sympathetic nerves supplying the heart and blood vessels, unlike those supplying the digestive tube, convey not inhibitory but excitatory impulses The excitement which inhibits the digestive processes, consequently, results in increased heart-rate and rise in blood pressure. The increased pressure is produced by the force propelling the blood into the arteries and the resistance to the outflow from them. Since sympathetic impulses both accelerate the heart-rate and constrict the arterioles, they bring about increased blood pressure by affecting both factors positively. The effect of even moderate excitement on blood pressure is unmistakable. As reported by Gallavardin and Haour (1912), the slight excitation incident to taking the blood pressure, in many cases, is sufficient to cause a rise of 25 to 35 mm. of mercury in the systolic level. In their experience, the first systolic reading was usually higher than those taken later in the same subject Schrumpf (1910) reported a case in which fear of a serious diagnosis caused a rise in blood pressure of 33 per cent When reassurance was given, the blood pressure promptly returned to normal. Fright, anger or pleasure, in extreme cases, may cause a rise of 90 mm. of mercury (Cannon, 1928)

In cases of so-called "soldier's heart" the slightest excitement or emotional stress usually results in a marked increase in the pulse-rate (130 to 150 beats per minute). The emotional stress incident to war may result in such sensitization of the sympathetic control of the heart, in these patients, that even mild stimulation produces extreme effects (Cohn, 1919).

In an experimental study reported by Bond (1943), in which changes in the cardiac rhythm in unanesthetized cats and dogs, startled by short, unexpected noises, were recorded electrically, it was found that these animals normally respond according to complex patterns of sudden high rises in heart-rate, beginning immediately after startle, followed by a sharp fall, a second rise of variable height and thereafter several undulations in rate until the response is terminated in two or three minutes. The response to adrenin appeared only after twelve seconds The cardiovascular responses to startle in dogs with the vagus and depressor nerves sectioned and the adrenals excluded were essentially similar to those of normal animals. Following section of the cardiac accelerator nerves and exclusion of the adrenals in both cats and dogs, startle was promptly fol-

lowed by vagus inhibition, resulting in moderate cardiac acceleration. These results suggest that profound cardiovascular disturbances may result from emotional excitation even in normal individuals and that the cardiovascular responses are mediated mainly through the sympathetic nerves.

Emotional disturbances tend to increase the output of sugar in diabetic patients. In many of them the degree of diabetes exhibited tends to vary in response to nervous and emotional influences. Emotional disturbances not infrequently are accompanied by low sugar tolerance and actual hyperglycemia even in the absence of diabetes. On the basis of quantitative determinations of the blood sugar in students before and after participation in intercollegiate athletic contests and scholastic examinations, Cannon (1915) pointed out that emotional disturbances exert a strong influence tending to bring about hyperglycemia in normal individuals. Inasmuch as the blood sugar is readily increased by sympathetic stimulation, it may be assumed that this influence of emotional stress is exerted through the sympathetic nerves. Although it is not clear that diabetes can be initiated through such sympathetic stimulation alone, the available data show clearly that any existing diabetes may be aggravated by emotional stress.

Emotional disturbances may also profoundly affect the visceral organs through influences on the thyroid gland. Marañon (1921) reported an extensive series of cases of hyperthyroidism brought on by emotional stress during war. That psychic and emotional disturbances are important etiologic factors in hyperthyroidism, in many cases, is a fact of common clinical observation. Any severe or unaccustomed emotional shock to the patient, furthermore, may aggravate the symptoms in a mild case and convert it into a severe one. Latent or potential cases of hyperthyroidism may be transformed into active cases by varying degrees of emotional shock. Although the thyroid gland cells are not innervated directly, sympathetic stimulation probably is a factor in producing the increased thyroid hyperactivity. The dominant symptoms associated with the disease also suggest the existence of autonomic dysfunction.

Many other visceral disorders brought about by the effect of psychic and emotional disturbances exerted through the autonomic nervous system might be mentioned, *e. g.*, disorders of menstruation, lactation, micturition, perspiration, etc. Indeed, every visceral function is subject to influences exerted by psychic and emotional states through the autonomic nerves.

The reactions of the visceral organs to an emotion may be regarded as the visceral contribution to the complete emotional state. Impulses emanating from the central autonomic centers in response to emotional stimulation result in the excessive discharge of adrenin and other hormones into the blood and the liberation of sugar to such an extent as to cause transient glycosuria. Energy is thus supplied for the muscular exertion which may be called for in possible physical combat or flight, particularly in emotions like fear, anger or rage. Under existing social conditions this autonomic defensive mechanism, in a large measure, is held in restraint. It has been assumed by some (Lueders, 1928) that repeated activation of this mechanism, if unsatisfied by instinctive expression, may result in an irascible or a fearsome disposition. Thus the visceral reactions to emotional stimuli, particularly in individuals with an unstable or hyperirritable autonomic system, would contribute to the causes of affective

disorders. Cannon and his associates, however, have shown that the discharge of adrenin is increased by muscular activity. The visceral concomitants of emotional excitement also persist for some time after the stimulus has ceased to act. On the basis of results obtained in animal experiments, Cannon and Britton (1927) attributed this to the continued discharge of adrenin due to the emotional excitement and its expression and emphasized the importance of limiting the expression of strong emotions, such as fear and rage, in order to avoid a persistent state of disquiet.

In view of the important rôle of the autonomic nervous system in visceral disorders, it is reasonable to assume that autonomic dysfunction, under certain conditions, may precipitate or maintain abnormal affectivity On the basis of an extensive study of gastro-intestinal reactions to emotions in patients with psychoses, Lueders (1928) advanced the opinion that protracted chronic emotionalism and morbid moods affect the visceral functions less and less but exert their greatest damaging influence at higher levels. The mental and moral faculties, consequently, become impaired and dominated by uncontrolled emotionalism, obsessions, hallucinations, etc Similar opinions also have been advanced by other investigators. In view of all the data available, psychoses cannot be regarded as merely abnormal functioning of the brain or central nervous system. They represent changes in the entire individual. Even under normal physiologic conditions, it may be assumed that the mind is influenced by the entire body, consequently, psychic processes are not limited to the cerebral cortex Affective behavior must be regarded as a function of the whole organism. The emotional life of the individual is determined in a large measure by the functional reactivity and balance of the autonomic nervous system.

Autonomic Factors in Psychoses.— *Definition.*—The psychoneurotic individual is one who is usually unable to achieve complete resolution of a tension or impulse without anxiety or inhibition and to execute the appropriate response, despite his possession of adequate equipment for successful mastery Psychoneuroses probably invariably are associated with autonomic dysfunction in some degree. Flynn (1937) advanced the opinion that problems which can be surmounted by the neurotic give rise to emotions in which the predominant physical manifestations are due to sympathetic stimulation and problems which cannot be surmounted give rise to emotions in which the predominant physical manifestations are due to parasympathetic stimulation. Bieber and Tarachow (1941) regard this concept as significant but prefer to think simply in terms of autonomic excitation and inhibition. According to their point of view, there is no advantage in attempting to correlate the specific nature of the problem with the specific autonomic symptoms. Any impulse or situation which cannot be normally mastered must give rise to some expression of this failure of mastery in the autonomic integration The specific autonomic symptoms vary from individual to individual. For example, failure of mastery in similar situations may be accompanied in one individual by diarrhea, in another by salivation, in another by conjunctival congestion, etc. These differences may be related to constitutional factors or physiologic states prevailing at the moment which not only play a part in determining whether mastery shall fail in a given instance but also in determining the nature of the autonomic response.

Schizophrenia.—In a study of autonomic integration in schizophrenia in which the autonomic status was determined by statistical analysis of the organic findings in 120 patients, Rheingold (1939) found the tendency toward a low oxygen consumption rate to be the most noteworthy abnormality. A state of general hypometabolism was prevalent in these patients as indicated by low blood pressure, a slight increase in the cholesterol content of the blood, low normal carbon dioxide combining power and secondary anemia. The low oxygen consumption rate, probably due to faulty regulation of cell respiration, appears to be an integral feature of the disease. Hypothyroidism was present in a high percentage of the cases and probably represents a factor in the pathogenesis of schizophrenia. This concept is not inconsistent with the fact that schizophrenics do not respond to thyroid feeding, since the thyroid hormone appears to act through hypothalamic mechanisms the dysfunction of which, in these patients, probably is a causative factor in the hypothyroid state.

Epilepsy.—The evolution of the epileptic seizure exhibits three phases: (1) the phase of prodromes or auras preceding the loss of consciousness, (2) the seizure proper, attended by loss of consciousness, and (3) the phase of recovery. All of these phases are attended by marked disturbances in autonomic functions. Those observed in the first phase include vasomotor, pilomotor, pupillary, secretory, cardiovascular, visceral, metabolic and emotional changes. The second phase, during which manifestations of widespread sympathetic stimulation are prominent, is essentially a catabolic phase. The heightened vasoconstrictor tonus in the peripheral areas, including the central nervous system, results in characteristic pallor, gradually giving way to a blush or frankly cyanotic discoloration of the face, with distention of the veins of the neck and forehead. The body temperature is elevated without relation to the severity or duration of the muscular spasm. Marked pilo-erection also is evident. These manifestations of sympathetic stimulation are most evident during the early part and at the acme of the seizure. The third phase, or phase of recovery, is essentially an anabolic phase, characterized by cholinergic energy restoring activity and recovery of the cerebrospinal functions which were in abeyance during the seizure. Parasympathetic stimulation is evidenced by contraction of the pupils, salivation, retardation of the cardiac rhythm and not infrequently by evacuation of the urinary bladder and the rectum. Cholinergic stimulation is further indicated by peripheral vasodilatation, profuse perspiration, a fall in blood pressure and a return to normal body temperature.

Epileptic seizures probably have their origin in central autonomic centers. Morgan (1930) advanced the opinion, on the basis of experimental and anatomical studies, that epilepsy frequently is related to chronic degenerative changes in the hypothalamus. Epileptic seizures also are more frequent symptoms of tumors in the vicinity of the hypothalamus than of tumors located in any other part of the brain. Epileptiform attacks, furthermore, may be induced by a sudden increase of pressure in the third ventricle.

The circulatory disturbance in the brain undoubtedly represents a fundamental factor in the causation of the convulsions during the epileptic attack. This conclusion, based on abundant clinical observations, is also supported by direct observation of the spasm of the cerebral vessels during

the seizure Changes in the CO_2 content of the blood as it affects the caliber of the arterioles and capillaries, the acid-base balance and the respiratory exchange, all of which play significant rôles in the phenomena of epilepsy, also are closely related to the responses of the cerebral vessels to sympathetic stimulation. The only constant phenomena in epilepsy, according to Orzechowski (1937), are the vasomotor manifestations in the pial and cerebral blood vessels.

The hypothesis that cerebral vasoconstriction plays a rôle in the causation of epileptic seizures is supported by both clinical and experimental data Foerster (1926), who observed the brain during intracranial operations while the patients were undergoing convulsive seizures, reported that the brain shrinks and then expands enormously with cyanosis of the pia mater. Spielmeyer (1930) reported histologic evidence of recurring vasospasm in the brains of epileptic patients. Jackson (1931) reported constriction of the retinal vessels during an epileptic seizure.

Penfield (1933) reported the arrest of visible pulsations of the arteries of the brain, which usually was wide spread, as the most constant vascular phenomenon associated with convulsive seizures induced by electric stimulation of the exposed surface of the brain during intracranial operations. In 4 of his cases the arrest of arterial pulsations was limited to a circumscribed area around the point of stimulation. The epileptic brain, according to Penfield, "is subject to vasomotor reflexes which have never been described in the normal brain" Inasmuch as sympathectomy failed to abolish epileptic seizures in certain of his cases, he concluded that the cerebral vasomotor spasm in these cases involved vasomotor reflexes which probably are not subserved by autonomic neurons located outside the cranial cavity. He advanced certain data which seem to support the hypothesis that some of these reflexes are subserved by neurons located along the cerebral vessels and by a local vascular nerve plexus which, on the basis of histologic studies, he has reason to believe is significantly increased in some cases. He advanced the opinion that "where such a lesion exists, excision of the local scar with its vascular plexus is at present the most effective way of abolishing these malignant local reflexes" Conclusive evidence of the existence of local reflex mechanisms along the cerebral vessels is not forthcoming, but focal constriction of cerebral vessels due to local lesions undoubtedly occurs (Cobb, 1938). This phenomenon cannot be abolished by interruption of the cervical sympathetic trunks but may be corrected in certain cases by excision of irritable areas in the cerebral cortex (White and Smithwick, 1941). Measurements of the flow of blood in the jugular vein before, during and after epileptic convulsions, reported by Gibbs, Lennon and Gibbs (1934), do not indicate widespread ischemia of the brain preceding or during the attack. In certain cases carotid sinus reflexes probably play a rôle in epileptic seizures (Marinesco and Kreindler, 1935).

Autonomic Factors in Headache.—The term, headache, as commonly used, may designate any one of a wide variety of aches and pains localized in the head. These symptoms are commonly associated with abnormal states of tension in the walls of the cerebral blood vessels (Northfield, 1938) Most headaches of intracranial origin, according to Pickering (1939), are associated with tension around the intracranial arteries, as may occur when these arteries dilate. Tension around the venous sinuses,

limb, following injection of one of the above solutions shows no marked reduction in the number of leukocytes although the rest of the peripheral area exhibits leukopenia This fact strongly supports the theory that the distribution of leukocytes is regulated through the autonomic nerves

Data obtained by Muller (1926) in two cases of insulin shock in diabetic patients indicate that while the peripheral vessels are dilated, the number of leukocytes in the peripheral blood is markedly increased The watery perspiration produced during this interval also indicates increased endothelial permeability In these cases the leukocytes in the peripheral blood reached 19 000 and 28 000 respectively in less than fifteen minutes and dropped to 7 000 the level which obtained before insulin treatment in less than ten minutes following the administration of glucose by mouth Simultaneously with the decrease of leukocytes in the peripheral blood the alarming symptoms produced by peripheral vasodilatation subsided thus showing that under these conditions the leukocyte curve runs parallel with the autonomic status at the periphery In a further experimental study Müller showed that general peripheral vasodilatation is accompanied by sympathetic hypertonus in the splanchnic region These data not only support the theory that the distribution of leukocytes is regulated through the autonomic nervous system but also indicate that endothelial permeability is modified by autonomic nerve impulses

The observation of Martin (1932) that exercise results in a marked increase in the number of leukocytes in the peripheral blood and that of Morias (1933) that cervical sympathectomy is followed by leukocytosis in the affected area are in full accord with Müller's findings In the counts made by Morias the polymorphonuclear leukocytes showed a marked increase whereas the other white cells showed no appreciable change in numbers According to Roesler (1933) the administration of atropine or calcium results in a change in the white blood picture of normal men in favor of the neutrophils whereas the administration of pilocarpine or cholin results in a change in favor of the lymphocytes The administration of adrenin in his experiments, resulted in the expected neutrophilia being marked by a preceding increase in the lymphocytes

In a study of the white cell changes under a variety of conditions (infection vigorous exercise pregnancy diabetic acidosis, etc) Hoff (1928) found not only that the distribution of leukocytes is subject to nervous regulation but also that the variations in the blood picture are closely correlated with other manifestations of changes in the functional balance of the autonomic nervous system particularly variations in the acid base balance He also maintained that the output of myelocytes by the bone marrow is increased by experimental sympathetic stimulation, while vagus stimulation results in relative lymphocytosis According to Rosenow (1928), stab wounds in the corpus striatum and hypothalamus cause neutrophilic leukocytosis but the temperature and blood curves do not necessarily run parallel In experiments on human subjects reported by Wossidlo (1935) diathermic stimulation in the region of the third ventricle resulted in leukopenia characterized by marked reduction in the number of polymorphonuclear neutrophils and little change in the numbers of other white cells

According to Petersen and Muller (1930) practically every insult to the organism is followed by rhythmic changes in the functional activity of

the organs, as is indicated by the leukocyte count and the chemistry of the lymph. For example, in their experiments carried out on dogs, external pressure on the eye sufficient to cause perceptible reflex cardiac inhibition applied for four minutes with repetition after five minutes was followed by a period of approximately seventy-five minutes during which the leukocyte count remained relatively low while the protein and calcium contents of the lymph were increased. After this, peripheral leukocytosis set in and the protein and calcium contents of the lymph were diminished. When ocular pressure was applied for two minutes and repeated at one-minute intervals, peripheral leukocytosis set in immediately with diminution in the calcium content of the lymph.

The results of experiments reported by Beer (1939) indicate a significant rôle of humoral transmission in the autonomic regulation of leukocyte distribution. In rabbits joined together parabiotically in pairs so that the peritoneal cavities were connected and only humoral transmission from one member of the pair to the other was possible, differences in temperature and in the numbers of white cells in the peripheral blood disappeared The rhythmic changes in the numbers of leukocytes also became the same in both animals Nerve stimulation which elicited leukocytosis in the animal to which the stimulus was applied resulted in a corresponding leukocytosis in the parabiotic partner

Splanchnoperipheral Vasomotor Balance During Chill and Fever.—In a clinical and experimental study, Petersen and Muller (1927) found that the functional balance of the splanchnic and peripheral autonomic mechanisms plays an important rôle in the symptoms of infectious diseases, particularly the chill and fever. Examination of the skin of a patient in a chill reveals pallor, pilomotor stimulation, transient perspiration and lowered temperature. The arterioles and capillaries are contracted The muscles exhibit tremor which varies greatly in intensity. These phenomena cannot be explained as the direct effect of a bacterium or the toxin produced by it on the peripheral tissue, but must be regarded as secondary effects of the toxic agent mediated through the nervous system

The results of Schottmuller's (1911) studies have shown that the chill is associated with the invasion of the blood stream by bacteria. He found that the chill was not caused by the mere presence of bacteria in the blood but takes place some time after the invasion (thirty to ninety minutes, depending on the individual and the type and number of organisms), *i. e.*, when the organisms or their toxic products have made contact with the body cells.

Muller and Petersen (1926) showed that the injection of bacteria, like the injection of peptone, salts, etc , results in profound alteration in the tonus of the blood vessels both in the peripheral and splanchnic areas, the splanchnic vessels being dilated and the peripheral vessels constricted. These diametrically opposite effects can hardly be due to the direct influence of the same toxic agent on the vascular endothelium or the neurovascular elements in both regions. More probably, the tonic state of the blood vessels is determined by the effect of the toxic agent on the nervous system, the splanchnic vessels being dilated in response to cholinergic stimulation in that region and the peripheral vessels constricted in response to adrenergic stimulation in the peripheral region That there is increased cholinergic activity in the splanchnic region during the interval of splanch-

nic vasodilatation also is indicated by the increased production of lymph with the onset of the chill This lymph arises in the splanchnic region, as is indicated by its high protein content (Petersen *et al*, 1923)

Petersen and Muller (1927) also pointed out that shock following perforation, acute pancreatitis, acute peritonitis indeed every insult to the peritoneum, such as ordinary laparotomy, etc leads to an alteration in the splanchnoperipheral autonomic balance with a redistribution of leukocytes resulting in splanchnic leukocytosis In the case of perforation the peripheral sympathetic and splanchnic parasympathetic orientation[1] is so pronounced that the peculiar "facies" may be regarded as more or less pathognomonic

In a study involving changes in the splanchnoperipheral balance Arquio (1928) pointed out a definite time relationship between altered tonus of the stomach and alteration in the peripheral leukocyte count When the gastric musculature actually is contracting the peripheral leukocyte count is increased during periods of gastric dilatation the peripheral blood exhibits relative leukopenia On the basis of this finding, he suggested that in certain pathological conditions which involve chronic gastric congestion and delayed digestion one should expect prolonged gastric dilatation to meet the physiologic digestive requirements and, consequently, a prolonged peripheral leukopenia

The findings of Müller and Petersen regarding the role of the autonomic nerves in the distribution of the blood volume in the peripheral and splanchnic regions is somewhat at variance with the so-called Dastre-Morat law, according to which the concentration of the blood in the splanchnic region due to paralysis of the splanchnic vasomotor mechanism as has been assumed to occur in shock is balanced by emptying of the peripheral blood vessels They have pointed out that when a limb is deprived of its vasomotor innervation by sympathectomy, its blood supply is not depleted, during shock by drainage into the splanchnic region They also have pointed out that the chill is not accompanied by paralysis in the splanchnic region but on the contrary by profound stimulation The splanchnoperipheral balance has become 'fixed,' with the splanchnic and peripheral regions oppositely oriented The effect of such fixation becomes apparent in the change in body temperature coincident with the onset of rigor or following it

Contrary to the current teaching they do not admit that heat production due to muscle tremor plays any part in the increase in body temperature The production of heat naturally is associated with an increased metabolic rate indicating increased activity of the splanchnic organs particularly the liver According to Petersen and Muller (1927), all the measurable functions of the liver are accelerated during the chill They found the output of bile and bile pigments measurably increased both in patients and experimental animals The reticulo-endothelium of the liver also takes up fat from the blood in one-half the time normally required (Jaffe 1927) Increased permeability of the capillaries and liver cells associated with this increased activity is evidenced by the fact that hemoglobin injected into

[1] Parasympathetic orientation as used by Petersen and Müller is not restricted to the functional state induced by stimulation of the parasympathetic nerves alone but indicates the functional state of organs in a region in which metabolism permeability blood supply action currents etc are increased Sympathetic orientation as used by these authors denotes the converse condition viz tissue rest

the blood stream during shock passes into the lymph at an increased rate and that bile pigments also enter the lymph stream

In further support of the theory that muscular tremor plays no part in the production of heat during the chill and that the rise in body temperature is due to heat generated by increased activity of the splanchnic organs, they advanced the results of animal experiments in which a condition approximating the normal human chill was produced by the injection of suspensions of living B. coli Muscle and rectal temperatures were recorded both by means of clinical thermometers and delicate thermocouples Constant leukocyte counts and observations on the lymph also were made In no case in which an actual chill was produced did they observe an increase in muscle temperature, although there was a sharp rise in the rectal temperature during the same interval A comparable, but greater, increase in temperature was noted in the liver. Not infrequently an actual reduction in muscle temperature took place during the rigor while the rectal temperature was rising This occurred even when there was no actual increase in the rate of heat loss at the periphery. An abrupt rise in temperature of the muscles was observed only at the end of the chill, usually when a coincident increase in the number of leukocytes in the peripheral blood indicated some vasodilatation in the peripheral region. On the basis of these results, Petersen and Müller concluded that no increase in the production of heat takes place with the shortening of the muscle during rigor and that delay in the warming of the muscles, despite a rise in the temperature of the rest of the body, must be due to an autonomic fixation in the muscles which prevents the dilatation of the arterioles and capillaries

The results reported by Petersen and Muller seem to indicate that profound alteration exists in the splanchnic and peripheral organs during the chill, brought about by the effects of a toxic agent on the nervous system which are exerted through the autonomic nerves The splanchnic organs are hyperactive, while the peripheral tissues are relatively inactive. Peripheral vasoconstriction, due to increased sympathetic tonus, reduces the loss of heat from the skin The work of Petersen and Muller seems to indicate that a similar condition obtains in the skeletal musculature during the chill On this basis, the skin, muscles and peripheral blood vessels may be regarded as a unit in their responses to the altered conditions of the body. Muscle tremor, therefore, may be regarded as indicative of increased splanchnic activity and heat production in the splanchnic organs. Conversely, increased splanchnic activity may produce muscle tremor If the increase in temperature takes place gradually, without the intense autonomic fixation apparent in chill, the tremor may not appear This probably explains why ordinary fever usually is not accompanied by chill

Autonomic Status of the Skin in Respiratory and Certain Other Infections.— In the general splanchnoperipheral interactions of the body the autonomic status of the abdominal and pelvic organs is opposed to that of the extraperitoneal organs and tissues, consequently, the autonomic status of the buccal and respiratory mucous membranes corresponds to that of the skin Under physiological conditions, particularly during bodily rest, the abdominal and pelvic organs are more abundantly supplied with blood than the extraperitoneal structures During muscular exercise or increased external temperature, the autonomic status is reversed and the splanchnoperipheral

blood volume ratio is shifted in favor of the peripheral structures When the body is exposed to low temperatures particularly in the absence of muscular exercise, peripheral vasoconstriction takes place and the skin becomes relatively ischemic Since the buccal and respiratory mucous membranes are similarly oriented, they also become ischemic According to Lehmann (1939), any measure which produces marked reduction in skin temperature elicits reflex nasal capillary constriction and any measure which causes marked elevation in skin temperature elicits reflex nasal capillary dilatation These reflex reactions are not limited to the nasal mucous membrane They undoubtedly possess temperature regulating value

Under ordinary physiological conditions, infective organisms are present on the skin and mucous membranes but, due to the local resistance infection does not take place Prolonged ischemia tends to reduce the local resistance and favors infection This is well illustrated in infections of the upper respiratory passages following exposure to low temperature or drafts That the reduction in the local resistance of mucous membranes is not a direct effect of exposure to cold is evidenced by the fact that if during such exposure, peripheral vasoconstriction is prevented by muscular activity, infection does not take place On the other hand respiratory infections not infrequently take place in the absence of any appreciable lowering of the temperature of the mucous membrane beyond that which is directly attributable to the local ischemia

Other infections of the mucous membranes *e g* herpes during fever or conjunctivitis occasionally seen during a flare-up of a localized pulmonary tuberculosis, undoubtedly are to be explained on the same basis They cannot be regarded as part of the primary infection but arise as a result of reduced local resistance due to the temporary ischemia of the tissue The exanthems of the acute exanthematous infections (scarlet fever, measles) undoubtedly also become possible because the resistance of the skin and mucous membranes to the circulating toxin is reduced due to the autonomic status at the periphery (Petersen and Müller 1930) Arsenical dermatitis following the administration of arsphenamine probably is to be explained in the same manner (Muller, Metz and Myers 1927)

The reactions which serve for the protection of the tissues when toxic substances have entered the skin or mucous membranes are characterized as inflammatory and depend on the autonomic status of the tissue as such Since these reactions involve local vasodilatation they are inhibited during the period of the general reaction to the infection which is characterized by peripheral vasoconstriction Following this period the tissues in the infected area become oppositely oriented, local vasodilatation takes place leukocytes accumulate in the capillaries and infiltrate the tissues tissue metabolism is accelerated and the local resistance is greatly increased The inflammatory reaction, therefore, differs only in degree from the normal physiologic response The direction of the change at the outset is the same in both cases

Autonomic Status of the Skin in Gastro-intestinal Infections —The more frequent occurrence of gastro-intestinal infections in warm climates and during hot weather than under other conditions is a fact of common clinical experience During hot weather the cutaneous blood vessels are dilated more or less constantly and the blood supply to the gastro-intestinal tract

is correspondingly diminished; consequently, the local resistance of the gastro-intestinal mucosa is reduced. The bactericidal properties of the gastro-intestinal tract, particularly of the duodenum and upper jejunum, are materially diminished during periods of peripheral vasodilatation (Arnold, 1929) According to Petersen and Levinson (1930), exposure to heat and high humidity, both in man and animals, results not only in diminished gastro-intestinal secretion but also in diminution in the normal response of the stomach and intestine to food According to their account, bacteria which under normal conditions are killed by passing through the stomach and duodenum of the dog passed through these divisions of the digestive tube alive, in most cases, when the dogs were kept in a superheated room Animals kept in superheated rooms usually died following the ingestion of meat poisoned with enteric toxins, whereas animals kept at normal or lower temperatures survived.

Man's susceptibility to gastro-intestinal infection, not only by fully virulent pathogenic organisms introduced into the digestive tube but also by the normal gastro-intestinal parasitic flora, always is notably increased at times of high external temperature. According to Arnold (1928), the gastro-intestinal flora undergoes a change in character as well as in range with increasing external temperature; the lower intestinal flora invades the upper regions of the gastro-intestinal tract

These changes do not necessarily depend on the actual height of the external temperature, but on the reactivity of the skin and the respiratory system at the time, as determined by their autonomic status The splanchnoperipheral imbalance usually is most marked at the beginning of the warmer periods of the year and when persons enter a tropical region from a colder climate Normal individuals usually are able gradually to become adapted to the higher temperatures Such adaptation involves a readjustment of the splanchnoperipheral autonomic balance This is of practical immunologic importance for tropical diseases as well as for a wide variety of ordinary gastro-intestinal infections.

Pulmonary Disease.—Tuberculosis —As previously stated, lesions of the autonomic ganglia have been described following death from tuberculosis. In an extensive clinical study of tuberculous patients, Deutsch and Hoffmann (1930) found parasympathetic tonus predominant during the second and third stages of the disease The hectic flush so common in the later stages of tuberculosis, but which does not appear early in the disease, probably is an expression of cholinergic stimulation exaggerated during intervals of marked activity of the disease process. The relatively slow heart-rate often observed during periods of fever, as compared with the heart-rate in other diseases during periods of the same degree of fever, also indicates exaggerated parasympathetic tonus. When the tuberculous process involves the intestinal tract, the discrepancy between the observed pulse-rate and that which would be expected with the degree of temperature present is still greater. According to Pottenger (1917), an unusual slowing of the pulse-rate in the course of pulmonary tuberculosis, coincident with an increase in temperature of 1° or 2° F., should be regarded as cause to suspect a complicating intestinal tuberculosis.

The gastric hyperacidity which not uncommonly occurs relatively early in the course of tuberculous disease also is associated with exaggerated parasympathetic tonus The patient's digestive powers may be above

par at first, enabling him to utilize relatively large amounts of food. The increased gastro-intestinal motility associated with the hyperacidity not infrequently results in nausea and a tendency to vomit. In some cases exaggerated parasympathetic tonus also results in spastic constipation. During toxemia in pulmonary tuberculosis, as pointed out by Pottenger, sympathetic tonus is increased due to central stimulation and the reflex effect of the inflammation in the lung; consequently, sympathetic tonus may predominate. As soon as the acute toxemia subsides and central sympathetic stimulation is diminished or ceases, a condition of relative parasympathetic hypertonus again obtains in the majority of cases. The patient's appetite is improved and his digestive powers are increased. As a rule, the associated gastric hyperacidity is not sufficient to cause discomfort; sometimes it actually causes gastric distress. Digestion usually becomes impaired more and more and stasis and constipation become more pronounced as the disease advances and toxemia and depressive emotional states become more marked. The gastro-intestinal symptoms commonly observed during the later stages of tuberculosis are less suggestive of parasympathetic hypertonus than those usually observed earlier in the course of the disease. In those cases in which parasympathetic tonus clearly predominates during the later stages of the disease, it may be due, as Stammler (1923) suggested, to depression of the sympathetic tonus by the toxic effects of mixed infection on the sympathetic ganglion cells. Sympathetic atony, according to Deisz (1929), indicates an unfavorable prognosis.

The data presented above indicate a succession of changes in the autonomic balance during the course of tuberculous disease which probably are in a measure conditioned by the constitutional tendency of the autonomic balance in the individual. The work of Glaser (1924) and Kading (1924) indicates parasympathetic hyperirritability in chronic tuberculous patients. According to Pende (1925), if a tuberculous patient first exhibits sympathetic hyperirritability and later parasympathetic hyperirritability, a grave prognosis is indicated, whereas if the patient exhibits primary parasympathetic hyperirritability, the disease usually runs a relatively benign course. On the basis of an extensive study of tuberculosis in children, Medowikov and Schenkmann (1932) have expressed the opinion that tuberculosis usually runs a benign course in children who, according to the pharmacodynamic criteria, exhibit parasympatheticotonia, whereas it usually runs a graver course in children who exhibit sympatheticotonia. They reported that nearly all the children with tuberculous meningitis, a highly fatal disease, in their series, exhibited parasympatheticotonia one or two weeks before death, as determined by the pharmacodynamic criteria.

Pigalew and Epstein (1930) have advanced experimental evidence in support of the theory that both the character of the local tuberculous lesions and the progress of the infection are influenced by autonomic nerve impulses. Organs which have a direct neurolymphatic connection with the central nervous system also react more intensely to local infection than those which do not. In their experiments, rabbits with abdominal tuberculous lesions showed increased capacity to combat the disease following section of both vagi below the diaphragm. In many instances, the lesions actually underwent regression. They, therefore, concluded that tubercu-

lous tissue which is freed from nerve impulses develops increased resistance to the infection This also is in keeping with the experience of laryngologists that cocainization of a tuberculous larynx to relieve pain not infrequently results in regression of the lesions. According to Ponomarew (1930), section of the vagus nerve on the infected side in rabbits with unilateral pulmonary tuberculosis retards the infectious process and tends to limit it to that side. It also tends to prevent intoxication of the vagus center. According to this author, the toxin produced in a tuberculous lesion poisons the nerve cells, resulting in trophic disturbances at the periphery and reduction in the capacity of the lungs to resist the infection. Trophic disturbances at the periphery in tuberculous patients also have been emphasized by Pottenger (1929, 1930), who described a large number of trophic reflexes arising in the pulmonary area and pointed out the significance of certain trophic disturbances in localizing tuberculous lesions in the lungs.

Histopathologic studies of tuberculous lesions in the human body indicate that the tissues react to tuberculous infection according to two modes: (1) the lesions may develop slowly and become quiescent through cicatrization and proliferation or (2) they may develop rapidly into exudative processes involving dissolution of tissues. These modes undoubtedly depend on differences in the irritability of the tissues. The greater the irritability, the more marked is the tendency toward an exudative process Tissue irritability obviously depends on the autonomic status, as defined by Petersen and Levinson, of the organism as a whole and of the various organs and its modifications by the infection

Petersen and Levinson have emphasized the importance of the reactions which take place in the zone of tissue stimulation which exists around every focus of tuberculous infection Within this zone, the effects of the toxin produced vary from slight irritation to cellular fatigue and death. During the stage of stimulation, tissue acidity and cell permeability are increased, metabolic processes are accelerated, calcium leaves the tissue, sodium and potassium enter it and tissue cohesion is reduced In general, this may be regarded as an abnormal status of the local functional balance in which the autonomic nerves, hormones, electrolytes and tissue metabolites all play their parts

The local reactions of the blood vessels constitute one of the most important factors in the progress of a tuberculous lesion. The reaction of the tuberculous tissue, as demonstrated by Schade and Clausen (1925), is on the acid side (pH 7 to pH 7.3) which is the optimum for the growth of the tubercle bacillus The toxin produced by the infection also causes dilatation of the blood vessels. In experiments reported by Preobraschewsky (1929), the dilatation produced by tuberculin in the vessels of uninfected animals was followed by contraction, but in the vessels of tuberculous animals the initial dilatation persisted indefinitely The vessels of tuberculous animals also showed reduced reactivity to adrenin. This is in keeping with the fact that adrenin causes little contraction of the vessels in an irritated or inflamed area or none at all

In the light of these experimental findings, it may be assumed that the tuberculin released at a focus of tuberculous infection causes local vasodilatation which, due to the failure of normal reversal to take place, becomes more or less permanent. The focal reactions, therefore, are

closely associated with the increased permeability of the dilated capillaries. For the same reason, clinical activation of tuberculosis not infrequently coincides with biological processes, such as the menstrual cycle, the effects of the season, etc., which are associated with an increase in capillary permeability and autonomic imbalance.

Since clinically advancing tuberculosis is associated with increased capillary permeability and healed tuberculosis with decreased capillary permeability, it may be assumed that increased capillary permeability, regardless of its mode of production, must influence tuberculous lesions unfavorably, whereas diminished capillary permeability favors improvement. In view of the significant rôle of the vasomotor nerves in the regulation of capillary permeability, the importance of clinical measures designed to restore the autonomic functional balance in tuberculous patients is indicated.

Bronchial Asthma.—The passage of air through the respiratory tract in inspiration and expiration may be hampered by contraction of the bronchial musculature, edema of the mucous membrane or excessive secretory activity of the bronchial glands. All these phenomena are related to the functional autonomic balance. Spastic contraction of the bronchial musculature involves neuromuscular mechanisms which normally play a significant rôle in the defense reactions of the upper respiratory tract. The efferent nerves involved are parasympathetic. They may be activated reflexly from the respiratory mucous membrane by impulses conducted centralward through vagus nerve fibers or from other parts of the body by impulses conducted centralward through other visceral or somatic afferent nerves. Edema of the mucous membrane of the respiratory tract represents a vasomotor reaction which may be elicited reflexly by afferent impulses arising in the respiratory tract or in other parts of the body. The bronchial glands are innervated through the parasympathetic nerves and respond reflexly to afferent impulses arising in other parts of the body as well as to impulses arising in the respiratory tract. The efferent nerves through which bronchoconstriction or vascular or secretory reactions in the mucous membrane of the respiratory tract are brought about may also be activated by impulses emanating from central autonomic centers. Asthmatic attacks associated with emotional states can be explained most satisfactorily on the assumption of hypothalamic stimulation.

The relative importance of spasm of the bronchial musculature, edema of the mucous membrane and hypersecretory activity of the bronchial glands in asthmatic paroxysms is not fully known. Evidence that each of these three factors plays a part is not wanting (Alexander, 1933). Bronchial asthma furthermore probably is invariably associated with parasympathetic hypertonus. The significance of hyperirritability of the vagus reflex arcs in certain cases of intractable asthma in the absence of recognizable etiologic factors is indicated by the beneficial effects of repeated bronchial relaxation brought about by means of sympathetic stimulation (Barach, 1943). The relief in these cases can be explained most satisfactorily on the assumption that a vicious cycle of bronchial spasm has been overcome by the repeated relaxation of the bronchial musculature.

In experiments reported by Braeucker and Kummell (1925), bronchial phenomena simulating asthmatic attacks were brought about in animals

(rabbit, ape) by stimulation of the medulla oblongata or the vagus or sympathetic nerves and by other experimental procedures These paroxysms did not occur following section of the bronchial rami of the vagi. This suggests that bronchial spasm resulting from sympathetic stimulation may involve reflex excitation of the vagus center due to stimulation of visceral afferent nerve components associated with the sympathetic nerves distributed to the bronchi. It seems not improbable, therefore, that relief of asthmatic attacks, in certain cases, following section or blocking of the sympathetic nerves to the lungs may have been due to interruption of reflex arcs comprising afferent spinal nerve components associated with the thoracic sympathetic nerves, ascending neurons in the spinal cord and brain stem and efferent parasympathetic neuron chains, including preganglionic vagus components.

In view of the important rôle of parasympathetic hypertonus in the phenomena of bronchial asthma, sympathetic stimulation may be expected to afford temporary relief due to its tendency to counteract the effects of parasympathetic stimulation Removal of the sympathetic influence by interruption of the sympathetic pulmonary nerves obviously is an irrational procedure. Rational treatment of asthmatic patients should include measures designed to restore the normal functional autonomic balance.

Pulmonary Embolism.—Pulmonary atelectasis has long been recognized as a postoperative and post-traumatic complication. Of all patients subjected to operative procedures, according to Scott (1925), approximately 3 per cent develop pulmonary complications of some kind Among these complications pulmonary embolism with consequent atelectasis or massive collapse of the lung are not uncommon. Various mechanisms have been suggested to explain these bronchial phenomena Most of the data available support the assumption that they are essentially reflex. Various investigators, particularly Schweigk (1935) and O'Shaughnessy (1936), have described respiratory and cardiovascular reflexes elicited by stimulation at the root of the lung The results of experimental studies reported by Jesser and de Takats (1941) also support the assumptions that the pulmonary vascular bed is richly supplied with sensory receptors and that the pulmonary vascular system possesses a potent sympathetic vasoconstrictor system The reactivity of the bronchial musculature to the stimulus of pulmonary embolism also is striking (de Takats, Fenn and Jenkinson, 1942). The mortality and morbidity of pulmonary embolism cannot be explained as the direct results of the mechanical plugging of the pulmonary artery but are due mainly to reflex effects on other thoracic viscera

On the basis of animal experimentation and clinical observations, de Takats *et al* (1942) advanced the opinion that the initiation of bronchial obstruction may be due to reflex bronchoconstriction and bronchosecretory activity which may subsequently result in mechanical occlusion. These reflexes appear to be elicited by the stimulating effects of distention of the vascular tree proximal to the obstructing embolus. Pulmonary embolism need not be regarded as the sole cause of atelectasis. Extensive atelectasis, even massive collapse of the lung may be caused by peribronchial pressure produced by tumors or by swelling of the mucous sheaths around foreign bodies, etc.

The reflex bronchial phenomena associated with pulm[illegible] bolism

represent reactions carried out mainly through the parasympathetic nerves. The vasoconstriction apparent in the lungs is mediated through the sympathetic nerves. The cardiac phenomena associated with pulmonary embolism suggest both parasympathetic and sympathetic reflex activity.

In view of the autonomic reflex activity involved in the phenomena associated with pulmonary embolism, it is apparent that pharmacologic agents which increase the flow of blood to the pulmonary arterial bed by increasing the output of the right ventricle, such as adrenin and digitalis, may be harmful, since an increase in pulmonary hypertension would tend to accelerate impending failure of the right side of the heart. Digitalis also exerts a sensitizing effect on the vagus reflex mechanisms. Drugs like atropine and papaverine should be beneficial since they tend to counteract the autonomic reflexes which originate in the affected lung. The usefulness of oxygen must be obvious, particularly in cases in which cyanosis is marked but vasomotor collapse is absent.

Nervous Regulation of Immune Reactions.—Production of Immune Substances.—The data set forth above regarding the autonomic nervous influences in the distribution of leukocytes and the permeability of the vascular endothelium strongly suggest that immunity and bodily resistance, in a large measure, are determined by the functional condition of the autonomic nervous system. The results of experimental studies also show that specific immune reactions are subject to nervous influences and that they may be initiated by specific reflex stimulation. In a series of experiments reported by Reitler (1924) the formation of antibodies was initiated in rabbits by injection of an antigen into the ear following ligation of its vessels. The ear also was amputated immediately (about three seconds) after the injection. This result shows clearly that the formation of antibodies may be initiated reflexly and that it may occur in the absence of antigen in the circulating blood. Bogendorfer (1927) reported the results of a series of experiments, carried out on dogs, in which he demonstrated that the production of agglutinin is influenced by impulses emanating from a central nervous center. The injection of a specific antigen which resulted in active agglutinin production in normal animals was without effect in his experiments in animals in which the spinal cord was previously transected in the cervical region. If the cervical spinal cord was transected after the production of agglutinin was initiated following injection of the antigen, the reaction continued. Transection of the spinal cord below the cervical region did not prevent the initiation of agglutinin production in response to the injection of antigen. Bogendorfer (1932) also advanced certain evidence in support of the theory that immune substances arise mainly in the reticulo-endothelial tissue. These data support the theory that the production of immune substances represents specific reflex secretory reactions to specific stimuli. They also show that an immune reaction once initiated may continue in the absence of nervous influences. The effector apparatus involved in the nervous regulation of immune reactions as yet is unknown.

Experimental data reported by various investigators, particularly Belak and his collaborators, indicate that both the sympathetic and the parasympathetic nerves play their roles in the regulation of the production of immune substances. In summarizing the results of investigations begun

before 1925, carried out by his collaborators and himself, Belak (1939) proposed classification of the immune substances, with respect to their relationships to the autonomic nerves, in two categories: sympathergic and parasympathergic The first category includes the essential non-specific antibodies, such as the alexins, opsonins, complement, etc, which are always present. Their production is augmented by sympathetic stimulation and inhibited by parasympathetic stimulation The second category includes the essential specific antibodies, such as antitoxin, precipitin, agglutinin, lysine, etc The production of these substances is augmented by parasympathetic stimulation and inhibited by sympathetic stimulation.

Other experimental and clinical data which support this point of view are not wanting In experiments reported by Illényi and Borzsák (1938), the hemolysin titer was increased by stimulation of the parasympathetic nerves, when the antigen was injected, and decreased by parasympathetic paralysis or stimulation of the sympathetic nerves. The effect on the hemolysin titer of sympathetic stimulation was more marked than that of parasympathetic paralysis. The onset of infectious disease, as indicated by fever, increased metabolism, leukocytosis, etc, is accompanied by sympathetic hypertonus, whereas during the period of recovery, as indicated by the return to normal body temperature, decreased metabolism, disappearance of leukocytosis, increased alkali reserve, etc. parasympathetic tonus gains the ascendency. At the beginning of an infectious process, therefore, resistance is decreased due to the increased sympathetic tonus which inhibits the production of the specific immune substances, whereas during the later phases resistance is increased due to increased parasympathetic tonus which augments the production of the specific immune substances (Frei, 1939, Hoff, 1942).

The non-specific immune substances, according to Belak, are related to the emergency functions of the sympathetico-adrenal system which responds automatically and promptly to psychic stimulation, pain, muscular exercise, blood pressure, cold and various other changes in the internal and external environments. The relationship of the immediate reactions to infection, intoxication, etc, to the sympathetico-adrenal system, therefore, is biologically significant The biological significance of the relationship of the production of specific immune substances to the parasympathetic system is less apparent.

The concept of the regulatory influence of the sympathetic nerves in the production of the non-specific immune substances and that of the parasympathetic nerves in the production of the specific immune substances, as formulated by Belak, undoubtedly expresses a fundamental biological relationship but cannot be regarded as strictly accurate in the light of our present knowledge of the anatomical distribution of the nerves of sympathetic and those of parasympathetic origin and the rôle of the neurohumoral mediators Belak's conclusion that the non-specific immune substances are related to the emergency functions of the sympathetico-adrenal system is well founded. The specific immune substances undoubtedly are related to cholinergic nerves both of sympathetic and of parasympathetic origin, which respond to cholinergic (parasympathetic) stimuli according to a common mode.

Allergic Disease —The common manifestations of allergy, such as hay fever, asthma, eczema and diverse anaphylactic reactions, probably are invariably associated with abnormal functional states of the autonomic nerves The latter may be induced by the tissue reactions to the sensitizing agent in question, but not infrequently the modified functional status of the autonomic nerves is a factor in the etiology of allergic disease The so-called 'allergic state' probably does not exist in the presence of a normal functional status of the autonomic nerves

The nature of the allergic state as yet is obscure A hereditary factor undoubtedly exists in many cases The observation of Landsteiner and Chase (1940), confirmed by Jacobs, Kelley and Sommers (1941), that a strain of guinea pigs which is resistant to a given allergen may be obtained by selective breeding strongly supports this point of view The hereditary factor may be concerned with the capacity of the organism to produce tissue antibodies the permeability of the tissue elements including the capillary endothelium or the release of substances such as histamine and acetylcholine, all of which processes may be influenced through the autonomic nerves

Emotional factors in the etiology of allergic disease have long been recognized These factors have gained increasing recognition during recent years in the causation of various allergic disorders As Gillespie (1936) pointed out, an asthmatic attack may occur as the accumulation of an anxiety, the expression of an emotional conflict, a protest against an unwelcome situation, a means of escape or as a conditioned response Urticaria of emotional origin is not uncommon Abramson (1942) reported the case of a woman aged thirty-one who while suffering from certain mental conflicts, developed giant hives after swimming in cold water The application of ice to her arm also resulted in the development of an urticarial wheal When later her mental conflicts were adjusted her sensitiveness to cold disappeared Numerous cases in which allergic symptoms of other types have been precipitated by emotional disturbances have been reported

The emotional factors in allergic disease emphasize the rôle of the central autonomic centers, particularly those located in the hypothalamus In a review of the nature of eczema Milian (1936) advanced clinical data in support of the assumption that the itching associated with this disorder is of central origin and that the associated capillary dilatation edema and secondary vesiculation are related to abnormal vasomotor function due to the low threshold susceptibility of these nerves to itching Lortat-Jacob (1937) also demonstrated definite association of the sympathetic nerves and pruritis erythema and vesiculation in the background of contact allergy He cited the case of a woman with more or less generalized eruption, caused by working with synthetic vanilla which was aggravated by pilocarpine and relieved by atropine The cutaneous lesions in this case obviously were related to reflex activity mediated through autonomic centers

The most spectacular of all allergic manifestations, protein anaphylaxis undoubtedly represents the results of the antibody-allergen reactions of the tissue elements Certain allergic manifestations, *e g* those of physical allergy, cannot be explained on the same basis A combination of heat, cold or sunlight with body proteins which could produce a new protein

would be difficult to visualize. In either case the functional disturbances bear essentially the same relationship to the autonomic nerves. They involve primarily tonic changes in the musculature of the visceral organs, including the vascular system. Since the tonus of the visceral musculature is regulated through the autonomic nerves, deviations from the normal tonic level of the visceral organs imply deviations from the normal functional autonomic balance. The changes in smooth muscle tonus commonly associated with allergic disease, *e. g.*, the heightened tonus of the bronchial musculature in bronchial asthma and the increased gastro-intestinal tonus and motility associated with various allergic diseases, indicate heightened parasympathetic activity The decreased vascular tonus, particularly in the shock tissue, commonly associated with allergic reactions are of the same order, although the efferent innervation of most of the blood vessels is mediated solely through sympathetic nerves The decreased vascular tonus may be explained in part on the basis of decreased activity of the adrenergic vasoconstrictor nerves and in part on the basis of increased activity of the cholinergic vasodilators. The increased secretory activity associated with allergic catarrhal inflammation of the nasal, pharyngeal and bronchial mucous membranes, the gastro-intestinal mucosa and the conjunctivæ also indicate exaggerated parasympathetic tonus The vasodilatation of the mucous membranes, indicating corresponding activity of the cholinergic vasodilator fibers, results in increased permeability of the capillary bed, which facilitates the discharge of serous fluid, thus providing the substratum for increased secretory output of the glands Increased capillary permeability due to vasodilator stimulation, in the absence of allergic disease, has been amply demonstrated. Activation of the glands in the mucous membranes, furthermore, is mediated mainly through the parasympathetic nerves Some of the most characteristic manifestations of allergic disease, therefore, are causally related to heightened parasympathetic or cholinergic reactivity.

Hyperreactivity of the cholinergic autonomic nerves associated with anaphylactic reactions in animals, in the absence of a preexisting autonomic imbalance, has been amply demonstrated. In experiments on cats reported by Heim (1940), the intravenous injection of a serum to which the animals had been sensitized three to five weeks previously resulted in a marked increase in parasympathetic tonus and reactivity of the parasympathetically innervated tissues.

The localization and the limitations of the shock tissue present intricate problems which probably will find their solution in a more complete understanding of the rôle of the cholinergic autonomic nerves in allergic reactions. The discharge of impulses through the parasympathetic or cholinergic nerves may be limited to a single organ or body region. This undoubtedly provides the physiologic basis for the fact that allergic reactions, as observed clinically, commonly occur in localized tissues known as shock tissues. The cholinergic influence in these reactions is indicated by the fact that, regardless of which shock tissue is affected, adrenin affords relief. The general adrenergic reaction tends to counteract the effect of the local cholinergic stimulation wherever the disturbance may be The experimental observation that the blood of rabbits in anaphylactic shock contains relatively large quantities of acetylcholine, whereas that of normal control rabbits contains none, supports this point of view.

Cardiovascular Disease —Nervous Factors in Abnormal Blood Pressure — Blood pressure and the supply of blood to the tissues depend mainly on the caliber of the blood vessels and the force and rate of the heart-beats Both these factors are regulated through the autonomic nervous system Under normal conditions, an increase in blood pressure elicits reflex cardiac inhibition, tending to restore normal pressure Under certain pathological conditions involving high blood pressure, the pressure may remain abnormally high and even mount still higher, although the heart is failing and the pulse weak The failure of the heart under these conditions, has been regarded by some as due to the high blood pressure If such were the case, lowering of the pressure would relieve the heart, which it fails to do It also has been suggested that as the output of the heart diminishes the tonus of the blood vessels is increased thus decreasing the size of the vascular bed to be filled If this reaction actually took place it might account for the maintenance of blood pressure at the normal level but not for a further increase in blood pressure while the heart is failing As is well known, one of the most powerful stimuli to the contraction of a muscle is its previous stretching The profound disturbance of cardiac rhythm resulting from pericardial effusion probably is due in a measure to interference with diastolic filling, and, therefore with the stretching of the cardiac muscle The marked hypertrophy of the left ventricle in aortic regurgitation undoubtedly is the direct result of increased work The stimulus for such increased work probably results mainly from the increased stretching of the muscle due to the filling of the ventricle both from the atrium and the aorta In like manner the diastolic stretching of the cardiac musculature due to raising the blood pressure by stimulation of the vasoconstrictor nerves in attempts to stimulate a flagging heart probably is an important factor in bringing about the desired cardiac response If the myocardium is diseased and the overstretched muscle fails to respond, such treatment must result in increased dilatation

The work accomplished by the heart even under normal conditions is relatively enormous On the assumption that the output of the heart is 2 5 ounces (usually it is more) at each contraction under conditions of normal blood pressure, the total output would amount to 7 5 tons of blood per day The work accomplished would be equivalent to lifting a ton of blood 122 feet In view of these figures it must be apparent that any increase in blood pressure adds materially to the amount of work required of the cardiac musculature, consequently anything which tends to maintain the blood pressure at an abnormally high level tends to deplete the cardiac reserve The increased blood pressure associated with advancing age not uncommonly plays an important role in shortening the remaining span of life due to the increased work required of the heart The rise in blood pressure nevertheless, must be regarded as a necessary conservative measure Attempts to lower blood pressure by means of vasodilator drugs, without attacking the cause of the rise, therefore, must be fraught with some degree of danger

Hypertension not uncommonly is associated with structural vascular lesions It often occurs in the absence of such lesions as a result of sympathetic stimulation The cause of such sympathetic stimulation sometimes is traceable to hygienic or dietetic variations sometimes to acute or chronic disease processes, and not infrequently to psychic and emotional

disturbances According to Lian, Stonesco and Vidarasco (1929), permanent arterial hypertension apparently of the idiopathic type is characterized by hyperexcitability of the vasoconstrictor nerves and hypoexcitability of the vasodilator nerves. Prolonged hyperactivity of the sympathetic nerves, whether resulting from the administration of adrenin in physiologic amounts or from the spontaneous emotional activity of the pseudoaffective state, according to Freeman (1933), results in a decrease in the volume of the circulating blood, involving both the liquid and the cellular elements. Prolonged vasoconstriction of itself, therefore, probably results in a loss of blood from the circulation

Hypotension often is more urgently dangerous than hypertension. The rôle of adrenin deficiency in abnormally low blood pressure is well known, particularly in Addison's disease. Adrenin deficiency probably always results in sympathetic hypostimulation. The cardinal symptoms of Addison's disease can readily be explained on this basis Hypostimulation of the cardiac accelerator and vasoconstrictor nerves, both of which are sympathetic, must result in corresponding atony of the entire cardiovascular system. The profound asthenia associated with adrenal insufficiency probably is due in part to vascular hypotension and in part to the relative atony of the skeletal musculature.

Hypotension also plays an important rôle in the phenomena of shock, but the various factors involved in this condition cannot be discussed in the present volume In view of the important rôle of the splanchnoperipheral vasomotor balance in the distribution of blood volume and the permeability of the vascular endothelium, it may be assumed that the vasomotor nervous mechanism plays an important rôle in the production of low blood pressure in shock as well as in various other disease processes

Carotid Sinus Reflexes in Disease —The innervation of the carotid sinus and the functional significance of the carotid sinus reflex mechanisms in the normal physiology of circulation and respiration have been outlined in Chapters VIII and IX In certain individuals in whom these mechanisms have become hyperirritable, stimulation of the carotid sinus not infrequently results in dizziness and fainting Such attacks may occur spontaneously or they may be induced by external pressure on the hypersensitive carotid sinus. In either case the symptoms are essentially identical. The same mechanisms probably play a rôle also in fainting associated with emotional disturbances in certain cases, a syndrome which Lewis (1932) designated "vagovagal" syncope Attacks of this kind occur not infrequently in apparently healthy persons as a result of stimuli such as the sight of blood, overheated and stale atmosphere or strong emotional reactions. They are accompanied by pallor, perspiration, fall in blood pressure, particularly the systolic, and frequently by bradycardia (Sutherland, 1927, Parker, 1928, Lewis, 1932; Ryle, 1934)

Fainting has quite generally been regarded as due to cerebral ischemia caused by a decreased cardiac output or by a temporary vasomotor collapse with consequent fall in blood pressure Temporary loss of consciousness is known to occur in various pathologic states such as angina pectoris, coronary thrombosis and various paroxysmal arrhythmias, in which the cardiac output is diminished and presumably cerebral ischemia results Weis and Baker (1933) have shown that temporary loss of consciousness may also occur without significant changes in blood pressure or heart-rate

in patients free of epilepsy or cerebral disease. In their cases, both the subjective and objective symptoms associated with spontaneous attacks could be duplicated by applying external pressure over the carotid sinus. The premonitory symptoms, such as weakness, dizziness and even convulsions without actual syncope, could be induced by varying the intensity and duration of the stimulation. In most of these patients fainting appeared to be caused by marked retardation of the ventricular rate with a consequent fall in blood pressure, or by a marked decrease in blood pressure without significant retardation of the heart rate, or by both. In some it appeared to be caused by cerebral vasoconstriction leading to anoxemia in the absence of significant changes in the heart rate or the blood pressure.

In a study of 315 cases encountered in cardiac clinics and private practice, carried out to determine the frequency of exaggerated carotid sinus reflexes and to ascertain their diagnostic significance, Sigler (1933) found these reflexes exaggerated most frequently in individuals with parasympathicotonic predispositions and more frequently in males than in females. Smith (1937) reported that carotid sinus syncope occurred in his clinic approximately five times as frequently in males as in females. He observed it most commonly in middle aged and elderly patients and rarely in the young. The chief symptoms, i. e., attacks of vertigo and intervals of unconsciousness with or without convulsions, are usually preceded by a definite aura characterized by weakness, lightheadedness, spots before the eyes and epigastric distress. In most of the patients attacks could be precipitated by external pressure on one or both carotid sinuses. Induced attacks frequently were accompanied by striking cardiovascular reactions such as retardation of the cardiac rhythm, varying intervals of cardiac arrest and paling of the face followed by flushing. Blood pressure usually was decreased but in a few instances there occurred a rise in blood pressure.

Grewe (1932) reported cases in which external pressure on the carotid sinus resulted in a very marked decrease in the heart rate and blood pressure and changes in the myocardial tonus. In some patients with high blood pressure the heart rate was reduced 25 per cent and the blood pressure 33 per cent. Premature heart beats also subsided or became much less frequent. Pulsus alternans in some cases disappeared completely. These clinical observations, according to Grewe, support the hypothesis of Wenckebach that the development and the character of the phenomenon known as pulsus alternans depends on the peripheral circulation. He also advanced the opinion that it is the result of a disturbance of the functional balance of the sympathetic and parasympathetic nerves, due to a sudden increase in endoarterial pressure. Pulsus alternans associated with paroxysmal tachycardia usually subsides as soon as the paroxysm is terminated. True pulsus alternans occurs most frequently in cases of cardiovascular-renal sclerosis, in many of which the myocardium also is affected. Other cases in which identical changes have been found never exhibit pulsus alternans. In those cases of cardiovascular renal disease in which it occurs, pulsus alternans usually is associated with a sudden increase in heart-rate and blood pressure, consequently it probably is invariably associated with a disturbance in the autonomic balance and should be regarded as a physiologic phenomenon and not as pathologic.

Hyperactive carotid sinus reflex activity not infrequently becomes further accentuated in the presence of local disease, e. g., sclerosis in the

carotid sinus, heart or vagus centers (Sigler, 1933) It is most accentuated in moderate bradycardia, diminished in tachycardia and absent in sinus bradycardia Of Sigler's patients, those with precordial pain exhibited exaggerated carotid sinus reflexes more frequently than those without such pain Under certain abnormal conditions other areas, including the eyeball, pharynx, larynx, bronchi, pleura, esophagus and arteriovenous aneurysms, may become sensory stations from which certain portions of the autonomic nervous system may be influenced in the same manner as from the carotid sinus (Ferris, Capps and Weis, 1937)

On the basis of the results of extensive investigations, particularly those of Weis, Ferris, Capps and their collaborators (1933–1937) carotid sinus reflexes may be classified in three main categories: (1) asystole or sudden retardation of the cardiac rhythm with or without a decrease in arterial blood pressure, (2) marked decrease in blood pressure without marked retardation of the cardiac rhythm; (3) cerebral circulatory alterations, causing fainting and sometimes convulsions, with or without marked changes in the cardiac rhythm or blood pressure.

Of the patients studied by Ferris, Capps and Weis (1935), a high percentage gave clinical evidence of vasomotor instability, such as palpitation, moist palms, skin sensitivity, etc The blood pressure tended to fluctuate spontaneously over a relatively wide range and the basal metabolism was low In some the hyperactivity of the carotid sinus mechanisms was associated with various functional and organic disorders such as emotional instability, cardiac disease and arteriosclerosis If associated morbid conditions are relieved by appropriate treatment the hypersensitivity of the carotid sinus mechanisms usually is reduced (Weis, Capps *et al* , 1936) The carotid sinus, however, does not appear to play a major rôle in the regulation of autonomic tonus (Ferris, Capps and Weis, 1937).

In any given case of exaggerated activity of the carotid sinus mechanisms, reflexes of one of the three categories outlined above play the major rôle, but those of the other categories are active in some degree. Fainting in which reflexes of the cerebral type predominate, however, bears no obvious relationship to retardation of the cardiac rhythm or the reduction in blood pressure Cerebral reflex vasoconstriction followed by compensatory vasodilatation has been demonstrated in such cases, but the vasoconstriction, according to Ferris, Capps and Weis (1935), cannot be regarded as the actual cause of the fainting but only as a concomitant manifestation, since the same or even a greater degree of cerebral vasoconstriction caused by adrenin does not result in fainting Observations on the cerebral blood flow before and during syncope, furthermore, fail to indicate marked vasoconstriction. The failure of oxygen to diminish the tendency to faint also militates against the theory of anoxemia due to vasoconstriction

The reflex activity of the carotid sinus mechanisms may be influenced by various pharmacologic agents Digitalis exerts a sensitizing effect on both the vagal and the cerebral reflex mechanisms The routine preoperative use of this drug, particularly in elderly patients, therefore, is contraindicated (Ferris, Capps and Weis, 1935) Both the vagal and depressor types of carotid sinus syncope can be controlled by adrenin or ephedrine. Atropine abolishes the vagal type but has no effect on the depressor type. Neither of these drugs exerts a marked effect on the cerebral type (Weis,

Capps *et al*, 1936) Surgical denervation of the carotid sinuses abolishes both spontaneous and induced attacks in suitable cases but exerts no influence on unrelated accompanying symptoms

Some Factors Involved in Pulmonary Engorgement and Hemorrhage —The pulmonary vessels like the systemic vessels, are subject to direct vasomotor control but not in the same degree The lungs also receive blood through the bronchial arteries which arise directly from the aorta In cases of hemoptysis involving only the pulmonary vessels, any measure which constricts the systemic vessels, *e g* the administration of adrenin may aggravate the bleeding by forcing blood from the systemic into the pulmonary vessels On the other hand, measures which bring about vasodilatation, *e g*, the administration of nitrites, tend to diminish the engorgement of the lung by diverting blood into the systemic vessels Hemoptysis due to necrosis of lung tissue may involve both pulmonary and bronchial vessels The former, being the more numerous are more likely to be eroded Yet even though a bronchial artery were the source of the hemorrhage the production of vasoconstriction by means of styptic drugs might still be harmful because a general rise in blood pressure and consequent turgescence of the lungs would tend to bring about hemorrhage at other weak points On the other hand measures which produce wide-spread vasodilatation might be beneficial because of their tendency to divert blood from the lungs which would also counterbalance the risks of reopening the bleeding point Lowered blood pressure would also favor the sealing of bleeding points by means of blood clots The relief of asthmatic attacks by the administration of adrenin probably is due mainly to its constricting effect on the vessels in the bronchial mucosa

Regulation of Cerebral Blood Pressure and Cerebral Hemorrhage —Since the cranial wall is rigid and the brain substance is incompressible the liquid content of the cranium consisting of the blood and cerebrospinal fluid is a constant volume If the volume of blood in the cerebral vessels is increased cerebrospinal fluid must be expressed from the cranium This is the first effect of a rise in arterial pressure in the brain The cerebral sinuses become compressed until the pressure in them equals that exerted against their walls by the brain substance Since the medulla oblongata contains vital centers its blood supply must be maintained at all hazards If the blood supply to the medulla oblongata becomes inadequate the resulting cerebral ischemia stimulates the vasomotor center to contract the splanchnic vessels This results in forcing more blood to the brain Dilatation of the splanchnic vessels on the other hand results in the withdrawal of blood from the brain The blood supply to the brain is controlled in a large measure by the vascular reactions of the splanchnic region which in turn is controlled by the vasomotor center in the brain

As shown by the results of animal experiments carried out by Cushing the general blood pressure must be kept at a level somewhat higher than that of the intracranial pressure in order to avoid cerebral ischemia When the intracranial pressure was increased by the introduction of a saline solution into the cranial cavity from a pressure bottle no effects other than a slight increase in the pulse and respiration-rates were observed until the intracranial pressure exceeded the blood pressure Even these effects could be avoided if the fluid did not affect the sensitive dura When the intracranial pressure exceeded the blood pressure, the splanchnic vessels

contracted and the blood pressure was raised until it again exceeded the intracranial pressure By repeatedly increasing the intracranial pressure the blood pressure was forced to a level above 200 mm. of mercury before the vasomotor center showed signs of giving way When the increased intracranial pressure was relieved, the splanchnic vessels dilated, bringing about a corresponding diminution of blood pressure If the vagi were divided before the intracranial pressure was modified, in these experiments, the blood pressure corresponded even more closely to the intracranial pressure, but always remained slightly higher than the latter That the adjustment of the blood pressure to the intracranial pressure was brought about by vasoconstriction in the rest of the body also was shown by the fact that no rise in blood pressure took place in response to increasing the intracranial pressure, following section of both the vagi and spinal cord

These experimental data have a practical bearing on the treatment of cerebral hemorrhage Measures designed to reduce the blood pressure to a level low enough to check the hemorrhage are fraught with danger because of the reduction of the blood supply to the medulla oblongata Furthermore, since the blood pressure is automatically maintained at a higher level than the intracranial pressure a vicious cycle is established, the hemorrhage increases the intracranial pressure, and the increased pressure causes a rise in blood pressure, which tends to increase the hemorrhage In general, a rising blood pressure in cerebral hemorrhage indicates a grave prognosis because it shows that the bleeding has not ceased Direct lowering of the intracranial pressure by means of a lumbar puncture tends to reduce blood pressure due to its effect on the vasomotor center, consequently, it tends to check the hemorrhage On the other hand, such lowering of the intracranial pressure is not without danger, in certain cases, since it reduces the support of the cerebral arteries and renders them more liable to bleed Since the blood pressure falls immediately following reduction of intracranial pressure the necessity for support of the arteries also is diminished.

On the basis of Cushing's experiments, it seems highly probable that, when more than one hemorrhage into the brain substance occurs, the smaller hemorrhages usually are caused by the effect of the larger primary hemorrhage on blood pressure The primary hemorrhage increases the intracranial pressure which, due to its stimulating effect on the vasomotor center, in turn raises the general blood pressure to a level at which the weakened arteries in other parts of the brain, particularly the pons, are unable to withstand the strain

Disorders of the Digestive Tract.—**Spastic Obstruction.**—Since the digestive tube receives inhibitory impulses mainly through the sympathetic and excitatory impulses mainly through the parasympathetic nerves, sympathetic stimulation results in retardation and parasympathetic stimulation in acceleration of gastro-intestinal activity. Any disturbance in the functional balance of the autonomic system, therefore, is reflected in gastro-intestinal activity

The functional activities of the esophagus seem to be dominated by its parasympathetic innervation. Under certain conditions, this division of the digestive tube reacts to nervous influences in a manner which affects the entire digestive system. In the case of a neoplasm near the cardiac orifice, the lower portion of the esophagus may become more or less per-

manently contracted and thus obstruct the passage of food into the stomach although the new growth, due to its small size, plays no mechanical role in the occlusion of the cardiac orifice Globus hystericus also involves spasm of the lower portion of the esophagus The actual point of constriction may pass up and down in the manner of a peristaltic wave The patient is unable to swallow yet no organic disease is present Constriction of the esophageal musculature is brought about by parasympathetic over stimulation In the case of globus hystericus, the cause of esophageal spasm is to be sought in a psychic disorder In most other instances esophageal spasm must be regarded as a reflex response to afferent stimulation For example malignant disease of the stomach may give rise to reflex contraction of the esophageal musculature In certain cases esophageal spasm constitutes the earliest objective evidence of organic disease of the stomach (Langdon Brown 1923)

So-called cardiospasm according to Hurst (1911), is not an active spasm of the cardiac sphincter but a failure of the sphincter to relax He proposed the term *achalasia* as more accurately descriptive of this condition The difference between achalasia and an active spasm is indicated by Hurst s observation that in the former condition a mercury tube in the esophagus can open the cardiac sphincter by its own weight Failure of the cardiac sphincter to relax undoubtedly is due in many instances to the conditions which excite active spasm in other parts of the digestive tube

The nervous control of the cardiac sphincter as Hurst and Rake (1930) pointed out is subject to four abnormal conditions vagus hyperactivity, vagus hypoactivity or paralysis sympathetic hyperactivity and sympathetic hypoactivity or paralysis Of these the second and third probably are the more important in cardiac sphincter dysfunction since vagus hypoactivity or paralysis may result in achalasia and sympathetic hyperactivity in cardiospasm On the other hand spasm of the cardiac sphincter may occur as a reflex result of acute inflammation or carcinoma of the lower portion of the esophagus peptic ulcer and possibly duodenal ulcer and gall bladder disease It probably does not occur as a purely functional disorder even in nervous individuals Hysterical dysphagia probably is due to disturbances in the neuromuscular control of the voluntary mechanism of deglutition which does not involve the cardiac sphincter

Pylorospasm may be brought about reflexly by a wide variety of causes *e g* gastric ulcer appendicitis renal calculus pyelitis and sometimes disease of the gall bladder or the genitalia Occasionally it occurs as a simple neurosis If the spasm is slight and of short duration it may be relatively unimportant but, if marked and persistent it results in gastric dilatation In some cases dilatation may be delayed for a long time by the initial compensatory hypertrophy of the stomach wall

Chronic appendicitis not infrequently is accompanied by mild ileal stasis which, according to MacLean (1932), is due to spasm of the ileocecal sphincter brought about by local irritation of the diseased appendix Gastro-ileal reflexes also play a rôle in the retardation of the passage of the contents of the small intestine into the cecum in chronic appendicitis These reflexes may be elicited by the introduction of food into the stomach In MacLean's study of 300 cases of chronic appendicitis, delay in the filling of the cecum was observed in about 50 per cent of the cases In his opinion,

this reaction is so characteristic that it may be regarded as a sign of chronic appendicitis.

Flaccid Obstruction.—Irritation of the peritoneum not uncommonly results in reflex inhibition of gastro-intestinal motility In acute general peritonitis, according to Robb (1932), the resulting sympathetic stimulation tends toward immobilization of the intestine, the purpose of which is protection of the lesion outside the gastro-intestinal tract, but which also results in intestinal stasis. In certain individuals with unstable autonomic balance, even slight splanchnic irritation elicits profound reflex inhibition of the intestine (Stout, 1933) Irritation of even a limited area of the peritoneum, therefore, may result in complete cessation of peristaltic activity and distention of the intestine due to loss of tonus of its musculature. Paralytic ileus sometimes follows abdominal operations in the absence of marked trauma or injury to the peritoneum, probably due to reflex inhibition elicited by impulses arising within the gastro-intestinal wall. Symptoms of flaccid intestinal obstruction, so-called ileus hystericus, arise in certain cases as part of the syndrome of hysteria. The intestinal inhibition in these cases undoubtedly is due to hypothalamic stimulation

Hypertrophies of Infancy.—On the basis of extensive clinical observations, Fraser (1926) advanced the theory that congenital hypertrophy of the pylorus, hypertrophic ileal obstruction and congenital hypertrophy and dilatation of the colon have their cause in autonomic nervous dysfunction. The essential lesion in congenital hypertrophy of the pylorus is a hypertrophy of the muscular coats of the pyloric canal and antrum and, to a slight degree, of the distal portion of the corpus of the stomach. This is essentially the portion of the gastric musculature which is concerned with the expulsion of the stomach contents. Roentgen-ray examination, according to Fraser, shows ill-timed and abnormal, yet forcible and prolonged contractions of the stomach, under these conditions, but the stomach content is not expelled. On the basis of his findings, he supported the theory, first enunciated by Thomson, that "the muscle is hypertrophied because from an early period in its development it has been worried into overgrowth by constantly recurring overaction, such as would result from even a slight degree of habitual incoordination " The underlying causes of this disease as yet are obscure, but the marked tendency of smooth muscle to undergo hypertrophy as a result of repeated forcible contractions is well known. The demonstrable abnormal activity of the hypertrophied muscle, furthermore, strongly suggests a functional cause The older theory of congenital redundancy is no longer tenable.

Hypertrophic ileal obstruction in infants usually involves the lower portion of the small intestine In 3 cases reported by Fraser (1926), the lower segment of the ileum approximately 6 inches in length was markedly hypertrophied, but the ileocolic sphincter was not involved. Above the hypertrophied segment, the ileum was markedly dilated On the basis of the findings in these cases, he advanced the opinion that this disease is similar in origin to congenital hypertrophy of the pylorus.

Congenital hypertrophy and dilatation of the colon resembles congenital hypertrophy of the pylorus and hypertrophic obstruction of the ileum both in pathology and in the fact that it involves a portion of the digestive tube on the proximal side of a sphincter. Usually the lower limit of the change is at the junction of the colon the rectum (O'Bei[illegible] sphinc-

ter). Occasionally, the hypertrophy and dilatation extend downward to the anal sphincter. This similarity and the fact that the disease first becomes evident in the weeks immediately succeeding birth strongly suggests a similar etiology. According to Fraser, the evidence in all the conditions suggests that the chief etiological factor is a neuromuscular error resulting in "an uncontrolled contractive function, a delay in the acquisition of the power of inhibition, combined it may be with achalasia and insufficient relaxation of the associated sphincters."

Intussusception.—If the above interpretation of the rôle of the autonomic innervation in the gastro-intestinal hypertrophies of early infancy is correct, it may be assumed that the distinctive feature of autonomic nervous dysfunction during the early weeks and months of life is localized hypertrophy. The autonomic dysfunctions of a later period are characterized by exaggeration of the normal functions of the gastro-intestinal musculature. Intussusception occurs most commonly during the period extending from the sixth month to the end of the second year but is not limited to childhood. Of 300 cases of intussusception operated upon in the Edinburgh Children's Hospital, according to Fraser (1926), 295 had their beginning in the lower end of the ileum where the original point of the invagination remained apparent after the reduction. The peristaltic rush consists of an advancing wave of contraction preceded by a wave of relaxation. As long as inhibition precedes contraction no harm can result, but if when the wave of contraction reaches the lower end of the ileum the inhibition phase is not transmitted due to failure of the inhibitory mechanism, the strong contraction of the peristaltic rush may carry a portion of the gut into the distal segment as an invagination, thus initiating the intussusception. According to Fraser intussusception occurs most commonly in cases in which the ileocecal segment has not become completely fixed to the posterior abdominal wall and is provided with a loose mesenteric attachment. There is no adequate reason to assume that this condition favors the initiation of intussusception although it offers a mechanical explanation of migration of the intussuscepting segment. The evidence strongly suggests failure of the coördinating mechanism controlling the ileocecal segment. In some cases intussusception involves only the ileum and in some only the colon. Intussusception of the appendix occurs only rarely.

Additional evidence that intussusception has its cause in disturbed autonomic control of the intestine has been advanced by Fulton, Kennard and Watts (1934) and Watts and Fulton (1934). In their experiments on monkeys and chimpanzees stimulation of the cerebral cortex in the rostral portion of the premotor area or bilateral extirpation of the cortex in this area caused excessive motor activity of the gastro-intestinal tract and not infrequently resulted in intussusception. These gastro-intestinal reactions obviously represent responses to excessive parasympathetic stimulation.

In many cases of gastric disorder the stomach itself is not at fault, but is made irritable by the reflex effects of a lesion elsewhere. Whenever gastric symptoms are strikingly intermittent it is safe to assume, in the absence of unmistakable evidence of a gastric lesion, that the lesion is located outside the stomach. In view of these considerations, it must be clear that if a patient can at times eat freely of any ordinary food without distress, and at other times rejects all food or suffers pain regardless of what he eats, the stomach itself probably is not at fault. Such intermittent attacks

not uncommonly are due to lesions of the gall bladder or the appendix. Some still maintain that gall stones may remain for years in the gall bladder without producing symptoms In general, this is untrue, unless the statement refers only to symptoms referable to the gall bladder Patients with gall stones commonly exhibit symptoms of intermittent gastric irritability A slight alteration in the position of the stone or a slight increase in the associated cholecystitis may at any time call forth violent reflex irritation of the stomach and spasm of the pylorus.

In general, it may be stated that the nearer the lesion is to the stomach, the more probable is the occurrence of reflex gastric symptoms Duodenal ulcer and gall bladder disease almost invariably call forth marked reflex gastric symptoms. Pancreatitis not only gives rise to reflex disturbances set up by the pancreatic lesion, but also results in inadequate neutralization of the gastric juice in consequence of diminished pancreatic secretion The symptoms associated with this condition, including those of intestinal obstruction, testify to the wide-spread sympathetic inhibition produced (Langdon Brown, 1923). Reflex gastric disturbances resulting from lesions farther removed from the stomach are less common but not infrequent

Just as spastic contraction of a sphincter or gastro-intestinal hypermotility may be brought about through the autonomic nerves, so a segment of the digestive tube may be inhibited, resulting in its dilatation Atonic dilatation of the stomach, brought about by sympathetic overstimulation, may explain many cases of chronic indigestion. Patients with this condition usually complain of feeling full as soon as they start eating because the dilated stomach cannot relax further, as the normal stomach does when food is ingested, consequently, the intragastric pressure rises. Fibrosis of the stomach gives rise to the same symptoms because also in this condition the stomach is incapable of relaxation. Obstructive dilatation of the stomach differs from atonic dilatation in that it usually is associated with powerful peristaltic waves under which the gastric musculature gives way but, in many cases, violent peristalsis still occurs after the stomach is enormously distended. Parasympathetic overstimulation obviously plays an important rôle in these cases.

Gastric and Duodenal Ulcers.—Gastric and duodenal ulcers commonly are associated with parasympathetic hypertonus As early as 1913 von Bergman expressed the opinion that the entire complex of nervous symptoms associated with gastric and duodenal ulcer is referable to autonomic dysfunction which manifests itself in vasomotor disturbances, resulting in ischemia and spasticity of the gastro-intestinal tract He regarded this as the real cause of the ulcerative process. Kaufmann (1913) regarded leukopenia as one of the signs of the constitutional disturbance responsible for gastric and duodenal ulcer He had previously called attention to a deficiency of gastric secretion as one of the contributing factors in the genesis of gastric lesions. More recently he also emphasized the rôle of gastro-intestinal spasticity which he regarded as a result of the underlying constitutional disturbance and not of the ulcerative lesion He also regarded psychic disturbances and overexertion of any kind as important factors in the genesis of gastric and duodenal ulcer. These observations regarding the rôle of vasomotor disturbances and leukopenia associated with gastric and duodenal ulcer become increasingly important in view of the evidence advanced by Muller (1926) that disturbances in the functional

autonomic balance are accompanied by regional changes in the permeability of the blood vessels and the distribution of leukocytes. According to Mucci (1926), ulcer formation is a direct result of a loss of functional balance between the sympathetic and parasympathetic innervation of the digestive tube which may be of emotional or toxic origin or both, but develops only with a constitutional tendency to gastro-intestinal neuroses. On the basis of extensive clinical and experimental studies Müller (1926) advanced the opinion that chronic gastric and duodenal ulcers have their cause in a chronic constitutional disorder one of the chief manifestations of which is a lack of balance between sympathetic and parasympathetic tonus. According to his view, slight irregularities in the general body economy, e.g., dietary indiscretions, psychic disturbances, exposure, etc., which under normal functional conditions of the autonomic nervous system give rise to visceral disturbances which are relatively unimportant and of short duration, may, if the functional balance between the sympathetic and parasympathetic nerves is already disturbed due to constitutional disorders, result in long-continued excitation of the hyperirritable components of the autonomic innervation of the organ in question. In individuals with parasympathetic hyperirritability, therefore, peripheral stimulation, e.g., sunburn, may result in gastro-intestinal hyperexcitation the duration of which cannot be foretold. Such peripheral stimulation according to Müller in certain individuals may actually give rise to gastric or duodenal ulcer. In individuals with chronic gastric or duodenal ulcer the underlying constitutional disorder likewise may give rise to periodic stimulation in the splanchnic area resulting in acute symptoms. The frequent recurrence of gastric and duodenal ulcer according to Müller also is referable to the underlying constitutional disorder. Berner (1932) and Stohr (1932, 1934) also emphasized the importance of underlying constitutional factors, particularly a labile condition of the autonomic nervous system, in the etiology of gastric and duodenal ulcers.

On the basis of extensive clinical experience and a review of the literature Cushing (1932) emphasized the role of the autonomic nerves in the genesis of peptic ulcers and pointed out the importance of influences emanating from the diencephalic autonomic centers. Intracranial lesions which affect the hypothalamus, particularly the tuber cinereum, or the conduction pathways leading from the hypothalamus to the efferent nucleus of the vagus, according to Cushing are prone to cause gastric erosions or ulcers presumably due to parasympathetic stimulation, possibly due to sympathetic paralysis. Intraventricular injections of pilocarpine or pituitrin in man in his experience caused an increase in gastric motility, hypertonus and hypersecretion leading to retching and vomiting with ultimate discharge of occult blood. Beattie (1932) also reported patches of hyperemia of the gastric mucosa in animals following direct electrical stimulation of the tuber cinereum. Pigalew (1932) advanced certain data which seem to support the view that gastro-intestinal lesions induced by lesions of the tuber cinereum occur most frequently in the pyloric portion of the stomach, the duodenum, the ileocecal region and the rectum. He advanced the opinion that the causation of such lesions rests on dystrophic nervous processes of a peculiar and constant form which are latent in the nervous system. Best and Orator (1932) failed to produce either acute or chronic gastric or duodenal ulcers in experimental animals by continued irritation of

the vagus with magnesium, nor did such irritation, in their experiments, prolong the healing of preexisting gastric or duodenal ulcers. Active inflammation of the gastric mucosa also failed to induce demonstrable pathological changes in the vagus nerves or the medulla oblongata.

In a study of 18 resected stomachs of patients with gastric ulcers, Stohr (1932) observed lesions of the enteric plexuses, involving mainly the ganglia and ganglion cells, in every case in which the disease was chronic. The degenerative changes in the enteric plexuses were most marked at the sites of the ulcerative lesions but they were apparent also in areas far removed from the ulcers. Whether the lesions of the enteric plexuses constitute a causative factor in the etiology of gastric ulcer or represent an accompaniment of the ulcerative lesions could not be determined On the basis of these findings and extensive clinical observations, Stöhr (1934) advanced the opinion that the causation of chronic gastric and duodenal ulcers is intimately related to dysfunction of the entire autonomic nervous system

Balint (1927) emphasized the constant association of hyperacidity with parasympathetic hyperirritability in ulcer patients and pointed out that most of these patients exhibit alkali retention, indicating an acid condition of the tissues The opinion that hyperacidity is an important factor in the causation of gastric and duodenal ulcers also is supported by a large volume of experimental data bearing on the production and healing of chronic peptic ulcers in animals Pepsin produced in the stomach probably also plays a significant rôle In both acute and chronic experiments on cats, Schiffrin and Warren (1942) found that perfusion of a segment of the gastro-intestinal tract with pepsin in an acid medium resulted in more severe ulceration than perfusion with acid alone They have emphasized the proteolytic action of the gastric juice as a factor in the etiology of gastric and duodenal ulcers

Under normal conditions the gastro-intestinal mucosa is not digested because it is not exposed to pure gastric juice One of the important factors in the protection of the mucosa against the corrosive action of the gastric juice is food. The pancreatic juice, gastric and intestinal mucus, duodenal secretion and bile constitute an additional mechanism by which the duodenal and, to some extent, the gastric and jejunal mucous membranes are protected When normal gastric juice is secreted in excessive quantities or continuously, in experimental animals, the neutralizing mechanisms are overcome and ulcer is produced (Dragstedt, 1942). Similar excessive secretion of gastric juice in man probably also results in gastric or duodenal ulcer. In most instances such hypersecretory activity probably is neurogenic As Dragstedt has pointed out, it is abnormal in the sense that it exerts its effect mainly while the stomach is empty and the usual stimuli for gastric secretion are in abeyance

In a study carried out on patients with duodenal ulcers, Berg and Thomas (1942) found that the neutralizing ability of the duodenal bulb was impaired but not wholly lost. They pointed out that ulcer patients differ from normal persons both in that the neutralizing capacity in the duodenal bulb is defective and the gastric secretion is hyperacid On the basis of an experimental study in which gastro-intestinal ulcerations were produced by the administration of pitressin, Berg (1942) emphasized the rôle of vascular alterations in the causation of peptic ulcers, particularly

in persons with a constitutional habitus characterized by vasomotor instability

Emotional factors in the etiology of gastric and duodenal ulcers have been emphasized by various investigators In a study carried out on ulcer patients and normal subjects Mittelmann and Wolff (1942) observed a rise in acidity and increased motility in the stomachs of all the ulcer patients and many of the normal subjects during periods of experimentally induced anxiety hostility and resentment On the contrary gastric acidity and motility were decreased in the same subjects during periods of induced feelings of contentment and well-being In reviewing the case histories of their ulcer patients Mittelmann and Wolff found that they had experienced prolonged emotional turmoil involving mainly conflict anxiety guilt hostility and resentment The recurrence of pain and in some cases hemorrhage was correlated with periods of special emotional stress

In a subject with a permanent gastric fistula through which the gastric mucosa could be observed directly Wolf and Wolff (1942) observed pallor of the mucous membrane and inhibition of gastric secretory activity and motility during emotions such as fear and sadness which involved a feeling of withdrawal During emotional conflicts involving anxiety hostility and resentment they observed increased gastric secretory activity hypermotility and hyperemia and engorgement of the gastric mucosa Intense sustained anxiety hostility and resentment were accompanied by prolonged increased secretory activity, hypermotility and engorgement of the gastric mucosa During these periods erosions and hemorrhages could be induced by the most trifling traumas Bleeding points also appeared spontaneously due to vigorous gastric contractions Direct contact of acid gastric juice with a small eroded area in the mucosa resulted in increased secretory activity and further engorgement of the entire gastric mucous membrane Prolonged direct contact of the gastric juice with such a lesion resulted in a chronic ulcer

The autonomic innervation of the stomach and duodenum also plays a rôle in the pain and distress associated with peptic ulcers In a study reported by Patterson and Sandweiss (1942) patients with duodenal ulcers recorded pain only when the duodenum was in an active phase of motility, regardless of whether the stomach was active or quiescent Epigastric pains of relatively long duration were invariably associated with exaggerated duodenal activity characterized by a state of increased tonus simulating incomplete tetanus Other factors in the production of ulcer distress are the site of the lesion the acid concentration in the duodenum, the relative abundance of pancreatic enzymes and bile and the potency of the duodenal hormones all of which are related to autonomic nervous function

In certain cases of acute peptic ulcer, treatment directed to the ulcer itself may be efficacious and the healing of the lesion may be regarded as terminating the disease In view of the various factors in the etiology of gastric and duodenal ulcers, particularly the autonomic nervous dysfunction, treatment, particularly in chronic cases should be directed to the patient as a whole since the ulcer is but a symptom of a more fundamental disorder This is in full accord with the long recognized clinical

teaching that chronic peptic ulcers cannot be cured by resection of the ulcerative lesions.

Colitis.—Mucous colitis occurs most commonly in persons who exhibit other evidence of autonomic instability Except in the presence of a primary infection, it is not an inflammatory condition but one which is fundamentally neurogenic The colonic musculature is highly irritable and not infrequently spastic Spastic contraction of one segment may result in distention of the more proximal parts, due to the retention of gas under pressure and pain The underlying cause of the pain may be either prolonged spasm of the musculature or stretching due to distention. Spasticity or stretching of the musculature results in limitation of the flow of blood in the mucous membrane with consequent ischemia and anoxemia of the tissue The mucus-secreting cells are stimulated and mucus is produced in large quantities The resulting clinical picture is one of alternating periods of constipation, pain and distention followed by periods during which mucus appears in large or small quantities with reduced constipation and occasional diarrhea. The ischemic condition of the mucous membrane tends to lower its resistance to bacterial invasion, consequently, the bacterial flora present may penetrate the wall of the colon and produce an inflammation which dominates the picture, but which must be regarded as a secondary phenomenon.

In certain cases of mucous colitis in which infection arises as a secondary phenomenon, this infection may result in ulcerative colitis In many cases of ulcerative colitis due to a specific infection the local condition of an irritable or spastic colon undoubtedly represents an aggravating factor which plays a significant rôle in the progress of the disease Nervous manifestations occur so frequently in ulcerative colitis that various investigators, including Murray (1936) and Sullivan (1936), have recognized neurogenic factors as significant in the etiology of the disease Others do not support this point of view but recognize the development of nervous manifestations in patients who gave no evidence of nervous instability previous to the onset of the disease (Jankelson, McClure and Sweetsir, 1942) Colonic lesions undoubtedly may give rise to nervous disturbances which in turn affect the progress of the disease

In view of the significance of autonomic nervous dysfunction in colitis, particularly in the absence of a specific infection, therapy directed toward the colonic lesions only is inadequate Efficacious treatment must be directed toward the patient as a whole.

Constipation—The propulsion of the intestinal contents distalward is influenced by various factors, including the character of the diet, the physiologic state of the enteric nerve plexuses and the influence exerted upon them through the extrinsic intestinal nerves, and reflex stimulation arising in other parts of the body Faulty propulsion in the large intestine usually is associated with overstimulation either of the sympathetic or the parasympathetic nerves Depressión of either division of the autonomic system also may result in motor dysfunction of the colon or rectum or both.

Propulsion of the colonic contents may be retarded due to lack of stimulating material such as roughage in the diet or due to reflex sympathetic stimulation which inhibits intestinal motility. Not infrequently constipation due to inhibition of intestinal motility is associated with disagreeable emotional states Constipation due to sympathetic stimulation may result

in the accumulation of relatively large quantities of fecal material in the colon and consequent distention of its wall.

Spastic constipation is a condition in which propulsion of the colonic contents is prevented or retarded by constriction of the lumen. It is commonly associated with an unstable or irritable condition of the colon. The unstable colon, as pointed out by Adler, Atkinson and Ivy (1941), is dyskinetic or dyssynergic. They have suggested the use of these terms as more accurately descriptive of the functional conditions in question than those commonly used. Spastic contraction of the colon obviously implies parasympathetic stimulation. The parasympathetic nerves in question may be activated reflexly due to stimuli arising within the gastro-intestinal canal. Carmichael (1941) has emphasized the importance of certain foods, allergies, foreign proteins, etc., as common causes of reflex spastic constipation. He also called attention to the importance of lesions in the anal area below the pectinate line, such as crypts, papillae and low hemorrhoids, as sources of impulses which elicit parasympathetic reflex activity of the colon. Fissures, hemorrhoids, etc., above the pectinate line, according to Carmichael, more commonly give rise to sympathetic reflex stimulation which may result in inhibitory constipation. Reflex symptoms of anal pathology are not limited to the colon but may involve more proximal segments of the gastro-intestinal canal and adjacent viscera, particularly the urinary bladder (Haydon, 1941).

Since inhibitory constipation implies sympathetic stimulation and spastic constipation implies parasympathetic stimulation, chronic constipation of either type implies a functional autonomic imbalance. Parasympathetic stimulation or sympathetic inhibition tends to counteract constipation of the inhibitory type whereas sympathetic stimulation or parasympathetic inhibition tends to counteract constipation of the spastic type. The importance of therapeutic measures directed toward restoration of the normal autonomic balance in the treatment of chronic constipation, therefore, is obvious.

Cutaneo-visceral and Viscero-visceral Reflexes.—The principle of counterirritation long recognized and applied in medical practice implies somato-visceral and viscero-visceral reflex activity. In a study of the effect on gastric tonus and motility of localized thermal stimulation of the skin carried out with the aid of the fluoroscope, Freude and Ruhmann (1926) found that such stimulation in the epigastric region elicited responses in the stomach within a few seconds. In general, cold applications first inhibit peristalsis but after a short interval stimulate irregular short peristaltic waves and at the same time bring about reduction or cessation of activity of the pyloric sphincter. Hot applications stimulate gastric peristalsis and bring about more frequent opening of the pylorus. A hyperirritable stomach is soothed, i.e., preëxisting hyperperistalsis is inhibited by hot applications. A preëxisting normal or subnormal gastric tonus is still further diminished by cold, but increased by hot applications. On the other hand, if the stomach is hypertonic its tonicity is still further increased by cold and inhibited by hot applications. In case of heterotonicity, the condition is aggravated by cold and alleviated by hot applications. In their experiments, gastric spasm was not appreciably influenced by cold nor relieved by hot applications. Neither did cold applications appreciably influence pylorospasm and consequent atonicity of the gastric musculature.

This condition was relieved by hot applications. In general, according to their findings, the effect on the stomach of cold applications is similar to inhibition produced by sympathetic stimulation, and that of hot applications to the effect of parasympathetic stimulation

Ruhmann (1927) showed that visceral reactions similar to those elicited by localized thermal stimulation of the skin may also be elicited by localized mechanical and chemical cutaneous stimulation and that the visceral response comes about only after a change in the tonic condition of the cutaneous blood vessels in the area stimulated has taken place The visceral organ affected, furthermore, undergoes a vasomotor change corresponding to the localized vasomotor change in the skin, i e, cutaneous hyperemia results in hyperemia and cutaneous ischemia results in ischemia of the visceral organs in question These findings are in full accord with the finding of Boas (1926) that bleeding of a gastric ulcer may be provoked by hot applications in the epigastric region

Bing and Tobiassen (1935) pointed out that stimulation within delimited cutaneous zones elicits reflex tonic reactions in the corresponding abdominal viscera which can be demonstrated by percussion Bing (1936) also described cutaneo-visceral reflex responses in the lungs which he regarded as the mechanisms involved in the therapeutic effect on these organs of hot applications to the skin Viscero-cutaneous reflexes elicited by the stimulating effects of pulmonary lesions, which may be of diagnostic value, have been described particularly by Pottenger (1929)

In a study of the vascular reactions in the viscera elicited by localized cutaneous stimulation, in decerebrated cats, Kuntz and Haselwood (1940) demonstrated, by means of photographic and plethysmographic records, that moderate cooling of the skin elicits reflex vasoconstriction and moderate warming of the skin elicits reflex vasodilatation in the corresponding portions of the gastro-intestinal tract The results obtained in this study also support the assumption that stimulation of the receptors involved in the cutaneo-visceral vasomotor reflexes is associated with changes in the tonic state of the cutaneous blood vessels Molander (1941) reported similar results of experiments carried out on dogs He also observed that hot applications inhibit, whereas cold applications stimulate gastro-intestinal motility. Cold applications also result in increased gastric acidity. He supported the opinion that ischemia in a visceral organ may give rise to pain due to the accumulation of a substance which stimulates the pain receptors, and that the relief of visceral pain by the local application of heat to the skin may be explained on the assumption that the reflex vasodilatation produced in the viscus results in reduction in the concentration of the pain stimulating substance to a level at which it is no longer effective

Certain clinical investigators, including Ludin (1919) and Boas (1926), have maintained that the effect on a visceral organ of heat applied to a localized cutaneous area is produced by increased temperature of the viscus due to direct penetration of heat through the tissues Many significant data do not support this theory For example, strong thermal stimulation of the skin in the epigastric region lasting for several hours does not result in a change in temperature of more than one degree in the stomach (Winternitz, 1871, Chelmouski, 1894; Iselin, 1911; Ludin, 1919). The fact that other means of stimulation which result in localized cutaneous hyper-

cium produce hyperemia in the corresponding viscera also militates against
this theory

The reflex character of the visceral responses to localized thermal
cutaneous stimulation furthermore is indicated by their segmental char
acter and the promptness with which the viscus responds when the stim
ulus is applied in the appropriate zone The fact that the vasomotor
change in the viscus corresponds to that produced in the cutaneous area
stimulated also indicates that localized cutaneous stimulation results in
like autonomic orientation in the cutaneous area and in the viscera inn
vated through the same segments of the spinal cord

In view of the facility with which cutaneous stimulation elicits refle
visceral reactions particularly vasomotor changes and changes in the
tonic state of the visceral musculature it must be apparent that many
visceral disorders particularly gastro-intestinal disorders may be influ-
enced beneficially by appropriate stimulation of the corresponding cutane-
ous area

Reflex responses in one viscus elicited by impulses arising in another
may be illustrated by the changes in the cardiac rhythm associated with
the introduction of liquids into the stomach Gastric distress associated
with lesions in other viscera e g the gall bladder is not uncommon
Viscero-visceral reflexes according to Sinelnikoff and Markeloff (1935) are
not limited to one or a few spinal segments but may involve widely sep-
arated segments of the body Patterson and Dunn (1911) have called
attention to the reflex influence on the stomach of impulses arising in the
urinary bladder In experiments carried out on dogs intravesical pressure
of 38 mm of mercury or over gave rise to one or more of the following
reflex effects in the empty stomach (a) reduction in the amplitude of the
contractions (b) complete cessation of motility (c) diminution of tone
(d) diminution of tonus with inhibition of motility (e) occasional slig
augmentation of motility The afferent impulses in question are conducte
mainly via the hypogastric nerves since the reflexes are not appreciabl
affected by section of the pelvic nerves

Inhibition of one segment of the gastro-intestinal tract may be elicited
by a sudden increase in pressure of 40 mm of mercury or over in another
segment A powerful contractile response may be induced in a segment of
the intestine following its sympathetic denervation by its sudden disten
tion This reaction must be mediated through enteric mechanisms since
it is not abolished by section of the vagi (Youmans Karstens and Aumann
1942) A significant feature of the regulation of intestinal motility through
extrinsic intestinal nerves according to Youmans *et al* is the reflex inhibi
tion due to stimuli arising from excessively strong contractions which
tends to keep the pressure within the intestine below the level at which i
would block the flow of blood through the vessels in the intestinal wall

CHAPTER XXII

AUTONOMIC NEUROSURGERY

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Introduction.—Surgical intervention involving partial or complete sympathetic denervation of a part or parts of the body has become a recognized therapeutic procedure in the treatment of patients with diverse diseases, particularly abnormal conditions in which limitation of the blood supply to the part in question is a prominent factor and conditions characterized by dysfunction of the visceral musculature or glands. Autonomic nerve section also is carried out for the relief of intractable pain of visceral origin, since the afferent conductors involved traverse the autonomic nerves.

In order to insure permanent physiologic results by sympathetic denervation, the operation must be anatomically complete and carried out in such a way that regeneration cannot take place. If the conduction pathways are not completely interrupted, the fibers which remain intact continue to conduct and the chemical mediator liberated at their terminations may activate not only the smooth muscle or gland cells with which they effect functional contacts but also adjacent denervated muscle or gland cells. Preganglionic neurons possess the capacity for regeneration in a remarkable degree The capacity of ganglionic neurons for regeneration is exceedingly limited Experimental data bearing on this problem are set forth in Chapter XVIII (p 401).

The physiologic effects of sympathetic denervation by ganglionectomy and by preganglionic nerve section, particularly with reference to the circulation, are set forth in Chapter V Since the vascular musculature becomes sensitized to adrenin in the circulating blood in a greater degree following degeneration of the postganglionic vasomotor fibers than following section of the preganglionic fibers, leaving the ganglionic neurons intact, sympathetic denervation by means of interruption of the preganglionic rami must be regarded as more advantageous than extirpation of the sympathetic ganglia The prevention of regeneration following operation is more difficult, however, in operations of the former type than in those of the latter. This applies particularly to operations carried out in the cervicothoracic region Smithwick (1940) described an operative procedure in which, following section of the communicating rami of the second and third thoracic nerves and division of the sympathetic trunk just below the ganglion in the third thoracic segment, the decentralized ganglia are covered with a silk cylinder, the lower end of which is drawn lateralward and sewed into the adjacent muscle. Various other methods of preventing the regrowth of preganglionic fibers into the ganglia have been attempted with varying degrees of success. The regrowth of preganglionic fibers into the superior cervical sympathetic ganglion can be effectively prevented by excision of a relatively long segment of the cervical sympathetic trunk Sympathetic denervation of the lower extremity by means of extirpation of the upper lumbar segments of the sympathetic trunk, as the operation is commonly carried out, is essentially preganglionic

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sympathectomy since the ganglia in which the sympathetic fibers to the extremity arise are left intact. The portion of the sympathetic trunk removed usually is long enough to render regrowth of preganglionic fibers into the lower lumbar and sacral sympathetic trunk ganglia improbable. Regrowth of preganglionic fibers into the celiac ganglia following section of the splanchnic nerves probably can be effectively prevented by excising segments of sufficient length or fixing the distal ends of the proximal segments into adjacent muscle.

With increasing knowledge of the anatomy and physiology of the autonomic nervous system surgery involving the autonomic nerves is emerging from its early uncertain and uncritical phase. Modern diagnostic methods afford adequate criteria for the discriminating selection of cases suitable for operation. Increasing knowledge of the type of operation required also is a significant factor in bringing about the desired physiologic effects.

Periarterial Sympathectomy.—The operation commonly known as periarterial sympathectomy consists in removing the adventitia with the nerve plexus contained in it from a segment of the vessel several centimeters in length. This operation has been employed in a wide variety of clinical conditions involving the blood supply of the extremities. The literature related to it is voluminous. A complete review of this literature in the present connection would be superfluous since the operation has during recent years quite generally fallen into disuse.

Jaboulay attempted denervation of certain arteries by cutting as many as possible of the nerves which approach them as early as 1899. In 1901 Higier recommended tearing the nerve plexus around the femoral artery in cases of intermittent claudication. Priority in periarterial sympathectomy involving the removal of a segment of the adventitia commonly is accorded to Leriche. Early in 1917 Leriche and Heitz reported 2 cases of severe causalgia of the median nerve following war wounds in which pain was relieved by resection of the sheath of the brachial artery. Later in the same year Leriche reported 37 cases of obstinate fractures and causalgia in which he divided the periarterial nerve plexus. He claimed complete success in 16 of these cases and fairly good results in some of the others in which the surgical treatment was followed by proper massage and muscle training. Since that time Leriche employed periarterial sympathectomy in a wide variety of clinical conditions. Although it has not given relief in all cases, he claims a high percentage of successes. According to published reports by himself and others (Penfield, 1925; Brüning, 1927; Leriche and Fontaine, 1933) this operation, in his hands, has been followed by success in cases of causalgia, Raynaud's disease, trophic and post-traumatic ulcers, various edemas and skin diseases, and a variety of other clinical conditions.

Periarterial sympathectomy was introduced in Germany by Bruning who with Forster (1922) reported lasting beneficial results of the operation in cases of Raynaud's disease and scleroderma. Bruning (1923, 1927) also reported beneficial results of periarterial sympathectomy in cases of trophic and vasomotor disturbances and in beginning gangrene. Various other investigators, including Kummell (1924), Rieder (1924), Stahl (1926), Polak (1926), Bittman (1926), Bailey (1928), Bernheim (1930), Cortes (1931), Colp, Kasabach and Mage (1933), and others have reported beneficial results of periarterial sympathectomy in certain cases, but also a high percentage of failures. Some who have carried out this operation and

observed its results in a variety of cases still regard it as a surgical procedure to be recommended particularly in cases in which an increased blood supply to the extremity promises relief, if the artery in question is not organically diseased. Others reject it both on the basis of observed results of the operation and the present status of our knowledge of the innervation of the peripheral arteries

The peripheral arteries, particularly those of the extremities, derive their nerve supply chiefly through branches of the peripheral nerves in proximity to which they lie These branches, which include both fibers of sympathetic and spinal ganglion origin, join the peripheral arteries at intervals throughout their entire extent (Chapter VIII). Although the periarterial nerve plexuses on the brachial and femoral arteries are continuous with the plexus on the aorta, offsets from the latter do not contribute materially to the innervation of the more distal portions of the peripheral arteries. Neither do long fibers extend distalward in considerable numbers even in the proximal portions of the periarterial plexuses associated with these arteries Periarterial sympathectomy, consequently, does not bring about sympathetic denervation of a peripheral artery

In view of the anatomic relationships of the nerves supplying the peripheral arteries, numerous attempts have been made to explain the beneficial results reported following periarterial sympathectomy. The immediate result of this operation, as observed by various investigators, is a primary stage of local contraction of the denuded artery which is followed by a secondary stage of vasodilatation associated with increased pressure, as compared with that of the opposite side, and a local increase of several degrees in skin temperature Later the vasomotor reactions revert to the preoperative state According to Leriche and Robeneau (1927), the results of periarterial sympathectomy are not due to section of efferent fibers alone but, at least in part, to reflex vasomotor phenomena which result in a general vasodilatation, with the most marked effect in the limb subjected to operation According to Colle and Pecco (1928), periarterial sympathectomy induces vasodilatation and hyperdistensibility of the vessels in the entire region dependent on the arterial tree which is the site of the intervention and sometimes also in neighboring regions, and lability of the arterial walls

According to Rogers and Hemingway (1930), the vasodilatation which follows periarterial sympathectomy in animals is very transient When this operation was carried out on the carotid artery in the albino rabbit, the resulting vasodilatation in the ear lasted about forty-eight hours. Comparison of the temperature of the limb following periarterial sympathectomy with that of the normal limb in the cat indicated no permanent vasodilatation

Not a few investigators have supported the theory that all the beneficial results observed, following periarterial sympathectomy, are due to hyperemia resulting from partial sympathetic denervation of the artery (Kappis, 1922, 1923; Kulenkampff, 1923, Drevermann, 1923, Seifert, 1922; and others). Others have supported the theory that periarterial sympathectomy results in a change in the tonic condition of the entire sympathetic system due to the reflex effect of stimulation of the sensory fibers supplying the artery (Lawen, 1922; W. Lehmann, 1924, Kümmell, 1923, Kreiblich, 1923; Polak, 1926; and others). Still others have advanced the opinion that the

hyperemia following periarterial sympathectomy is due to stimulation o short duration caused by section of the small fiber bundles along the artery (Kreuter, 1923, Rieder, 1924, E P Lehmann 1924) On the basis of the results of microscopic studies of the capillaries Magnus (1926) opposed the theory that the changes observed following periarterial sympathectomy are due to reflex effects of the operation and advanced the opinion that the local increase in temperature is a result of traumatic disturbance of the circulation Weidhopf (1923, 1924) correlated the hyperemia following operation with a preceding ischemia Brüning (1927) advanced the theory that interruption of the periarterial nerve plexus which is made up mainly of nerve components which join the artery through branches of the spinal nerves and maintains a tonus which may be regulated through the vasoconstrictors results in a lowering of this tonus and consequent hyperemia Fraser (1931) supported the theory advanced by Leriche and Fontaine (1927) that the hyperemia is in part a result of incomplete denervation of the artery and in part the result of afferent impulses which induce a general vasodilatation

The subsidence of pain following periarterial sympathectomy as reported in certain cases is no less difficult of explanation on the basis of our present knowledge of the innervation of the peripheral arteries than the occurrence of hyperemia Gundermann (1923) like Leriche supported the theory that the subsidence of pain is a result of improved circulation and nutrition Brüning (1924) and Drevermann (1923) regarded it as a result of the absence of angiospasm W Lehmann (1924) explained it on the basis of reflex inhibition of the vasoconstrictors in consequence of the removal of centripetal stimuli from the artery or raising of the threshold of stimulation of the sensory fibers supplying the artery or both Certain other investigators particularly Friedrich (1924), Schilf and Stahl (1925) and Abrashanow (1927) have advanced experimental data in support of the theory that some sensory fibers supplying a peripheral artery run longitudinally in the periarterial plexus They have assumed that the partial subsidence of pain following periarterial sympathectomy, in certain clinical cases is due to the cutting of these sensory fibers

None of the theories cited above seem adequate in the light of our present knowledge to explain either the occurrence of hyperemia or the subsidence of pain following periarterial sympathectomy Some degree of peripheral vasodilatation undoubtedly is a fairly constant result of this operation The reports of its beneficial results betray overenthusiasm in many instances but the alleviation of pain in certain cases can neither be denied nor disregarded It must be conceded nevertheless that there is no rational anatomic or physiologic basis for this operation as a clinical procedure The results reported in the literature furthermore do not justify its continued use

Sympathetic Ganglionectomy and Ramisection —Definition and Review —Sympathetic ganglionectomy consists in the removal of one or more ganglia of the sympathetic trunk in order to insure complete interruption of all peripheral connections Sympathetic ramisection consists in section of the communicating rami connecting one or more ganglia of the sympathetic trunk with the spinal nerves Surgery of this type is not new Alexander (1889) performed bilateral extirpation of the superior cervical sympathetic ganglion Jacksh (1892) resected the vertebral plexus and divided

the sympathetic trunk between the middle and inferior cervical ganglia Jaboulay (1896) divided the sympathetic trunk both above and below the middle cervical ganglion in cases of epilepsy and performed sympathetic ganglionectomy in a case of exophthalmic goiter Jonnesco (1897) carried out a similar operation in a case of glaucoma Ball (1899) extirpated the superior cervical ganglion in a case of glaucoma with atrophy of the optic nerve The results of these early operations were unimpressive and did not stimulate interest in surgery involving autonomic nerve section or gangli-onectomy Stimulated by Franck's (1898) discussion of the incidence of angina pectoris in cases of acute exophthalmic goiter and his suggestion that anginal pain may be due to an overflow from the spinal cord of im-pulses from the cardiac plexus which reach the cord via the inferior cervical and first thoracic sympathetic ganglia, Jonnesco, in 1916, first performed sympathetic ganglionectomy for the relief of anginal pain. Following his lead, not a few surgeons became interested in the surgical treatment of angina pectoris, with the result that sympathetic ganglionectomy became a recognized clinical procedure in the treatment of angina pectoris in selected cases

The publication in 1924 by Royle and Hunter of their findings in exper-imental animals and the clinical results of sympathetic ganglionectomy and ramisection in cases of spastic paraplegia gave a tremendous impetus to the study of the functional relationships of the autonomic nervous system and led to the application of surgery involving the sympathetic system in a wide variety of clinical conditions. One of the most important results of this work, on the clinical side, is the extensive application of sympathetic ganglionectomy and ramisection in the treatment of diseases in which circulatory disturbances in the extremities are pronounced

During the past two decades surgical intervention has been carried out involving nearly all parts of the sympathetic division and certain parts of the parasympathetic division of the autonomic nervous system. Many and diverse surgical procedures have been described, a complete account of which cannot be included in the present volume The parts most commonly involved in surgery are the sympathetic trunks, the splanchnic nerves, the celiac, renal and inferior mesenteric plexuses and the hypogastric nerves. Vagotomy, denervation of the carotid sinuses, partial extirpation of the pulmonary plexuses and section of the pelvic nerves have been carried out in some cases. In the light of present knowledge of the anatomy and physiology of the autonomic nerves, the physiologic results of a given surgical procedure can be anticipated with some degree of certainty

Surgery Involving the Sympathetic Trunks.—As it has been practiced in the past, surgical interference with the sympathetic trunk usually has involved extirpation of one or more ganglia with the intervening inter-nodes This procedure insures complete sympathetic denervation of areas supplied solely through the ganglia in question In certain areas there is sufficient overlapping of the distribution of sympathetic fibers arising in adjacent segments that extirpation of the ganglia in the segments in ques-tion does not insure complete sympathetic denervation

Equally complete functional sympathetic denervation can be obtained by section of the preganglionic fibers alone, leaving the ganglia and the gray communicating rami intact Preganglionic sympathectomy of this kind is practiced by various surgeons in order to avoid sensitization of the

sympathetically denervated structures to adrenin in the circulating blood. Preganglionic sympathectomy may be regarded as preferable to ganglionectomy wherever the regrowth of preganglionic fibers into the ganglia can be effectively prevented. This is particularly difficult in the segments involved in the sympathetic innervation of the upper extremities.

Cervical Sympathectomy.—Resection of a segment of the cervical portion of the sympathetic trunk may be regarded as the procedure of choice to prevent the conduction of impulses from the superior cervical sympathetic ganglion. This operation probably effects complete sympathetic denervation of the eye. It does not insure complete sympathetic denervation of the cephalic area, since sympathetic fibers arising as low as the inferior cervical or stellate ganglion enter the head via the plexuses on the common carotid and vertebral arteries. It also eliminates but a small portion of the sympathetic innervation of the heart. To insure complete sympathetic denervation of the head the operation must extend low enough to insure interruption of the conduction pathways from the inferior cervical or stellate ganglion to the plexuses on the common carotid and vertebral arteries or section of the corresponding preganglionic fibers.

Cervicothoracic Sympathetic Ganglionectomy, i.e., extirpation of the inferior cervical and upper two or three thoracic segments of the sympathetic trunk, has been practiced extensively, particularly for sympathetic denervation of the upper extremity. In operations of this type it is desirable to include the third thoracic segment of the sympathetic trunk, since in a large percentage of cases sympathetic fibers arising in the ganglion in the second thoracic segment reach the brachial plexus via an intrathoracic ramus of the second thoracic nerve which joins the first (Kuntz, 1927) and in a somewhat smaller percentage sympathetic fibers arising in the ganglion in the third thoracic segment reach the brachial plexus through the same ramus via a ramus arising from the third thoracic nerve which joins the second (Kirgis and Kuntz, 1942).

In order to avoid the undesirable effects of extirpation of the inferior cervical or stellate ganglion, particularly Horner's syndrome and sensitization of the vascular musculature to adrenin in the circulating blood due to degeneration of the postganglionic vasomotor fibers, and still obtain functional sympathetic denervation of the upper extremity, Telford (1935) advocated section of the white communicating rami of the second and third thoracic nerves and crushing and division of the sympathetic trunk below the third thoracic ganglion, leaving the white communicating ramus of the first thoracic nerve, the sympathetic trunk ganglia and the gray communicating rami which join the brachial plexus intact. Smithwick (1936) advocated section of the roots of the second and third thoracic nerves proximal to the communicating rami and removal of a short segment of each nerve, and section of the sympathetic trunk below the level of the third thoracic ganglion, leaving all other connections intact. These procedures are based on the assumption that preganglionic components of the first thoracic nerve play no significant part in the sympathetic innervation of the upper extremity.

This assumption has been supported by various investigators. According to Gask and Ross (1937), the preganglionic fibers involved in the sympathetic innervation of the upper extremity traverse the thoracic nerves from the fourth to the ninth inclusive. With the aid of the pleth

ysmograph, Foerster (1939) obtained data which he interpreted as indicating the presence of sympathetic preganglionic fibers for the upper extremity in the third to the sixth and possibly the seventh thoracic nerves. On the basis of results obtained in experiments on Rhesus monkeys in which action potentials of the peripheral nerves elicited by stimulation of the ventral nerve roots were recorded, Sheehan and Marazzi (1941) reported limitation of the preganglionic outflow for the upper extremity to the fourth to the eighth thoracic nerves inclusive, with the major outflow in the fifth, sixth and seventh Geohegan *et al* (1942) found no preganglionic fibers for the hand in ventral nerve roots above the fourth thoracic in the monkey and none above the third thoracic in the cat On the basis of experiments on human subjects in which the changes in cutaneous resistance were recorded during stimulation of anterior nerve roots, Ray, Hinsey and Geohegan (1943) reported preganglionic fibers for the hand commonly present in the second to the fifth thoracic nerves and in some instances as low as the tenth In one of 18 subjects they recognized evidence of such fibers in the first thoracic nerve According to their findings, stimulation of the preganglionic fibers in any one nerve root elicits secretory activity of sweat glands in all the fingers Failure to interrupt the preganglionic fibers in only one segment, therefore, would vitiate the clinical results in the treatment of peripheral vascular disease

In an experimental investigation carried out on cats and dogs, Kuntz, Alexander and Furcolo (1938) found that stimulation of the ventral roots of the first thoracic nerve elicited vasoconstriction in the distal parts of the limb and activation of the sweat glands in the paw pads With the stellate ganglion and the gray communicating rami connecting it with the brachial plexus left intact, in their experiments, complete sympathetic denervation of the upper extremity could not be effected without interruption of the white communicating ramus of the first thoracic nerve

Since these results are not in complete agreement with those cited above and in view of the importance of complete sympathetic denervation of the upper extremity in various clinical conditions, as indicated by the reported failures to achieve complete functional elimination of the sympathetic nerves, particularly in the distal parts of the upper extremity, in certain clinical cases in which the white communicating ramus of the first thoracic nerve, the stellate ganglion and the gray communicating rami connecting it with the brachial plexus were left intact, Kuntz and Dillon (1942) carried out a further series of experiments on cats and Rhesus monkeys, with the aid of the photoelectric plethysmograph, to determine the presence or absence of preganglionic fibers in the first thoracic nerve which are functionally related to the sympathetic innervation of the upper extremity.

The photoelectric plethysmograph is a convenient device for recording changes in the volume pulse wave, particularly in the distal segments of the digits, due to reflex vasoconstrictor stimulation, and is highly sensitive. In the experiments reported by Kuntz and Dillon, the stimulus (ice or faradic stimulation) was applied to one of the other extremities while the volume pulse waves in the finger or toe pads were being recorded With the animals under nembutal anesthesia, records were taken before operation, after removal of the second and third thoracic segments of the sympathetic trunk, leaving the communicating rami of the first thoracic nerve and the stellate ganglion intact, and after removal of the stellate

ganglion and the second and third thoracic segments of the sympathetic trunk (Figs 89 and 90)

Application of ice to the soles of the feet or mild faradic stimulation of the femoral nerve, in both cats and monkeys elicited marked vasoconstriction in the digits of the upper extremities with intact innervation. Following extirpation of the second and third thoracic segments of the

FIG 89 —Photoelectric plethysmographic records from toe pads of the upper extremity of a cat under anesthesia induced with soluble pentobarbital made after unilateral extirpation of the second and third thoracic segments of the sympathetic trunk leaving the cervicothoracic ganglion and its connections with the first thoracic nerve and the brachial plexus intact *A* upper record from the side on which operation was done lower record from the other side The stimulus was ice applied to the hind feet *B* upper record from the side on which operation was done lower record from the other side The stimulus was faradic stimulation in the femoral region Stimulation was begun at the first marker and discontinued at the second (Kuntz and Dillon Courtesy of Arch Surg)

sympathetic trunk, ice applied to the soles of the feet sometimes and faradic stimulation of the femoral nerve always elicited vasoconstriction in the digits of the upper extremity on the operated side Following extirpation of the stellate ganglion and the first and second thoracic segments of the sympathetic trunk, the same stimulation usually failed to elicit any change in the volume pulse waves in the digits of the affected extremity In a few instances, particularly in the monkey, a slight degree

of vasoconstriction could be elicited in certain of the fingers, probably due to the presence of sympathetic fibers which join the brachial plexus from the nerves in the vertebral canal (Van Buskirk, 1941), which had not been interrupted

The technic employed in these experiments obviates the criticism which may be raised against the results of experiments in which ventral nerve roots are stimulated directly The recorded changes in the volume pulse waves, furthermore, cannot be due to increased output of adrenin, since no record of volume pulse changes in the digits could be obtained following complete sympathetic denervation of the extremity The results of these experiments fully corroborate the earlier findings of Kuntz, Alexander and Furcolo cited above and seem to demonstrate conclusively the presence of

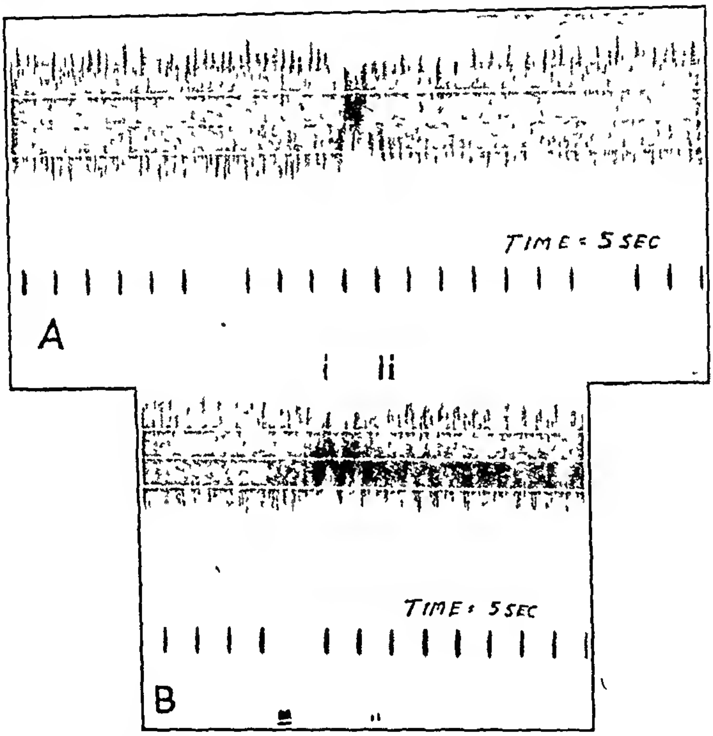

FIG 90 —Photoelectric plethysmographic records from finger pads of a Rhesus monkey under anesthesia induced with soluble pentobarbital *A*, before operation, *B*, after extirpation of the second and third thoracic segments of the sympathetic trunk. Faradic stimulation in the femoral region was begun at the first marker and discontinued at the second (Kuntz and Dillon Courtesy of Arch Surg)

some preganglionic fibers in the first thoracic nerve which are involved in the sympathetic innervation of the distal parts of the upper extremity. If the distribution of the preganglionic components of the first thoracic nerve in the stellate ganglion in man is comparable to that in the monkey complete sympathetic denervation of the upper extremity obviously cannot be accomplished by any operative procedure which leaves the preganglionic components of the first thoracic nerve, the stellate ganglion and its gray communicating rami intact

Cervicothoracic sympathectomy, including the upper three thoracic segments of the sympathetic trunks, eliminates the major portion of the sympathetic innervation of the thoracic viscera. Complete sympathetic denervation of the heart and lungs can be effected by extending the operation low enough to include the lowest sympathetic trunk ganglia from

which nerves enter the cardiac and pulmonary plexuses. Except in rare instances, such extensive thoracic sympathetic denervation cannot be regarded as either practical or desirable.

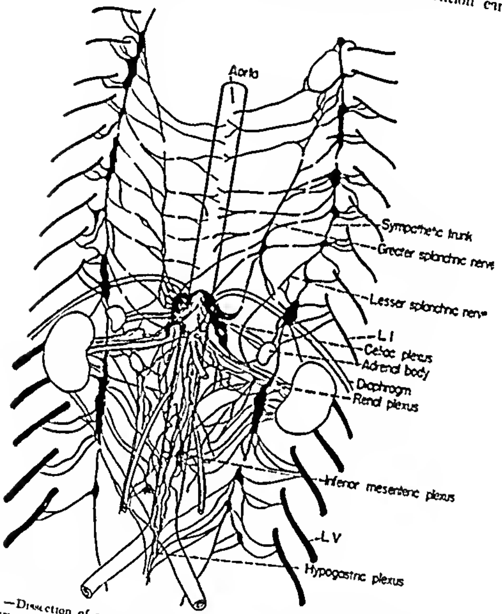

Fig. 91.—Dissection of sympathetic nerves in man, redrawn from Stiemens (1934), to illustrate origin from the sympathetic trunks of nerves to abdominal and pelvic viscera, with interruptions to indicate resections designed to eliminate sympathetic innervation of splanchnic vascular bed and lower extremities.

Lumbar sympathetic ganglionectomy as commonly carried out involves extirpation of several lumbar segments of the sympathetic trunk. With respect to the lower extremity and the innervation of abdominal and pelvic organs through postganglionic fibers arising in the sacral sympathetic trunk ganglia it is essentially a preganglionic operation, since no preganglionic fibers enter the sympathetic trunk below the second or third lumbar segment. As indicated by the extent to which the blood flow is increased and the duration of the vascular improvement, as reported by many observers

the results of this operation in the lower extremity have been more satisfactory than the results of cervicothoracic sympathetic ganglionectomy in the upper extremity. This difference probably can be explained most satisfactorily on the assumption that the vascular musculature becomes sensitized to adrenin in a lesser degree in the presence of intact postganglionic fibers in the lower extremity than following degeneration of the postganglionic fibers in the upper extremity.

Splanchnicectomy.—Splanchnicectomy consists in interruption of the preganglionic fibers to the ganglia of the celiac, superior mesenteric and other plexuses associated with the abdominal aorta and its branches Section of the splanchnic nerves arising from the thoracic and upper two or three lumbar segments of the sympathetic trunk alone does not effect complete functional sympathetic denervation of the abdominal and pelvic organs, since numerous splanchnic rami comprising mainly postganglionic fibers arise from the sympathetic trunk in the lower lumbar and sacral segments. In the cat, according to Harris (1943), approximately 3,000 postganglionic sympathetic fibers converge upon the inferior mesenteric plexus Complete functional sympathetic denervation of the abdominal and pelvic organs can be accomplished by section of the splanchnic nerves and extirpation of the lower thoracic and upper two or three lumbar segments of the sympathetic trunks Regrowth of preganglionic splanchnic fibers into the ganglia in question can be effectively prevented by resecting segments of the splanchnic nerves as long as possible, particularly those arising above the extirpated portion of the sympathetic trunk. Operative technics employed in splanchnicectomy have been described by various surgeons including Craig (1934), Peet (1935), Allen and Adson (1940), and Smithwick (1940).

Presacral Neurectomy.—Resection of the hypogastric plexuses is carried out particularly for the relief of intractable pain of pelvic origin This operation does not effect complete sympathetic denervation of the pelvic viscera, since the sacral and some of the lower lumbar sympathetic rami join the pelvic plexuses directly It probably interrupts all the visceral afferent fibers associated with the sympathetic nerves which reach the pelvic viscera. These obviously include most of the fibers which conduct impulses of pain from pelvic visceral receptors, since pain of pelvic origin has been relieved in many instances following this operation. In cases of extensive pelvic disease, particularly malignancy which involves the parietal peritoneum or other somatic tissues, the conduction of painful impulses is not limited to the hypogastric nerves

Resection of the inferior mesenteric plexus with the superior portions of the hypogastric plexuses has been advocated particularly by Rankin and Learmonth (1930) for sympathetic denervation of the distal portion of the large intestine in cases of congenital megacolon. This operation does not effect complete sympathetic denervation of the descending colon for the same reason that resection of the hypogastric plexuses does not completely eliminate the sympathetic innervation of the other pelvic viscera.

Vagectomy.—Bilateral resection of the vagal connections with the posterior pulmonary plexuses was first carried out by Phillips and Scott (1929) for the relief of bronchospasm of neurogenic origin. Reinhoff and Gay (1938) reported bilateral resection of the posterior pulmonary plexuses in cases of severe asthma. This operation undoubtedly eliminates the major portion of the parasympathetic innervation of the bronchial muscu-

ness of sympathetic denervation but the methods for inhibiting vasoconstriction or promoting vasodilatation previously referred to are not well adapted for the detection of minor variations in surface temperature. The finger plethysmograph (Bolton, Carmichael and Stürup, 1936) and the photoelectric plethysmograph (Hertzman, 1937, 1938, Smithwick, 1940) afford more effective means of detecting the presence of intact vasomotor fibers. These methods probably are more sensitive but less accurate in the localization of limited areas of incomplete sympathetic denervation within the larger area affected by the operation than the methods which depend on the detection of perspiration.

CHAPTER XXIII

AUTONOMIC NEUROSURGERY (CONTINUED)

PERIPHERAL VASCULAR AND CARDIAC DISEASES

Peripheral Vascular Disease.—Anatomic and Physiologic Considerations.—Peripheral vascular disease is characterized by limitation of the blood flow through the peripheral vessels due to hypertonus or spastic contraction of the vascular musculature or partial occlusion of the vessels due to local lesions In either case two major processes are at work. (1) obstruction of the arteries and (2) development of collateral circulation Either of these processes may become dominant The former is essentially damaging; the latter reparative (Montgomery, Waide and Freeman, 1941) Hypertonus or spasm of the vascular musculature is mediated through the vasomotor nerves which may be activated reflexly or by impulses emanating from central autonomic centers Since the peripheral vasomotor nerves are sympathetic, interruption of the peripheral sympathetic conduction pathways must effectively abolish responses of the vascular musculature to nerve impulses in the affected area If limitation of peripheral circulation is due to organic obstruction of arterial vessels, the vascular musculature may exhibit hypertonus in some degree Sympathetic denervation of such vessels results in increasing the flow of blood through them to the extent that the lumina are increased due to blocking of the tonic nerve impulses If the collateral circulation is highly developed, the blood supply to the part in question may be markedly increased following sympathetic denervation even though the effective lumina of the partially occluded vessels are not appreciably enlarged

Although complete sympathetic denervation of an extremity results in paralysis of its vasomotor nerves, the increase in the flow of blood observed immediately after operation is not maintained at the same level. Restoration of tonus in blood vessels following a period of relative atonicity immediately after sympathetic denervation is a common physiologic phenomenon Sensitization of the vascular musculature to adrenin in the circulating blood following degeneration of the postganglionic vasomotor fibers may result in a relatively high degree of tonus which, according to certain investigators, reaches its maximum in eight to ten days and then gradually subsides (Simmons and Sheehan, 1937) Studies involving measurements of the blood flow in extremities of experimental animals following sympathetic denervation do not support the assumption that it remains above the normal level but for a relatively short time.

In experiments carried out on dogs in which the volume flow of blood was approximately equal in both femoral arteries before operation, Herrick, Essex and Baldes (1932) found the minute volume in the femoral artery on the side of the operation approximately double that on the opposite side following unilateral lumbar sympathectomy In experiments reported by Johnson, Scupham and Gilbert (1932), the blood flow in the extremity had returned to the preoperative level twenty-one days after sympathectomy. According to observations extending over a long period,

as reported by Essex, Herrick, Baldes and Mann (1943), the flow of blood in the left hind limb of a dog was approximately double that in the right ten months and twenty-five days after left lumbar sympathectomy, but after nine and ten years it was approximately equal in both hind limbs. The vessels in the left hind limb were profoundly sensitive to adrenin both nine and ten years after operation, whereas those of the right hind limb reacted normally to adrenin. Histological examination of the digital vessels ten years after operation revealed marked hypertrophy of the arteriolar muscle in the left limb, whereas the arterioles in the digits of the right limb showed no hypertrophy.

In experimental animals the temporary increase in circulation of a limb following its sympathetic denervation results in a rise in surface temperature and increased redness in any cutaneous area in which the color is not obscured by pigment. Sympathectomy in man also commonly results in a rise in surface temperature and increased redness of the skin in the areas affected. In a careful calorimetric study of the extremities following lumbar sympathetic ganglionectomy, Brown and Adson (1925) found a marked increase in the production and radiation of heat in the legs and feet. Heat production and heat conduction in the feet were increased 200 to 900 per cent. The skin temperature of the feet was increased 2° to 6° C. Determinations of skin temperature of the legs and feet before operation showed a decrease toward the periphery. After operation this condition was reversed, the feet became relatively warmer. Perspiration also was absent. Similar alterations in skin temperature and heat elimination following sympathectomy in cases in which the blood supply to the extremities was diminished before operation have been reported by many investigators.

In the animal experiments cited above, the volume blood flow in sympathectomized extremities gradually returned to approximately the preoperative level. The vascular tonus regained after paralysis of the vasomotor nerves by sympathectomy obviously did not exceed the normal preoperative tonus. In man, if the vessels of an extremity are constricted before operation due to exaggerated vasomotor tonus, there is no reason to assume that they will contract beyond their normal calibers in the readjustment following removal of the vasoconstrictor influence; consequently, the blood supply to the extremity may remain permanently increased.

Preoperative Tests.—In the selection of patients for treatment by sympathetic denervation the determination of the capacity of the vascular bed to transmit more blood is one of the most important factors. Surface temperature determinations afford a useful index if interpreted with reference to the conditions of external temperature and humidity under which they are made. On very hot days or in the presence of fever the capacity for normal peripheral vasoconstriction is lost and skin temperature tests are of no value. At ordinary temperatures the normal vasoconstrictor gradient increases toward the periphery so that the fingers and toes are the coolest points on the surface of the body. Removal of the tonic influence of the vasomotor nerves results in abolition of the temperature gradient in the extremities and all parts of the body surface reach approximately the same temperature level. Morton and Scott (1930) have designated the maximum vasodilator response of normal arteries as

"the normal vasodilatation level" In extremities in which the vasoconstrictor nerves have been released by elevating the body temperature or by regional or general anesthesia the lower limit of this level may be taken at 86 5° F When the room temperature is 68° F., the temperature at the tips of the fingers and toes should rise to 90° F or over If this does not occur, organic vascular disease may be suspected (White and Smithwick, 1941). The total rise in the skin temperature of a given digit, following vasomotor inhibition, is less significant as an index of the capacity for vasodilatation than the proximity to which the rise approaches the normal vasodilatation level The magnitude of the former response depends in part on the initial temperature of the extremity; the latter is a measure of the degree of arteriolar dilatation.

The preoperative tests commonly used to differentiate between limitation of the flow of blood by vasospasm and by narrowing of the arteries due to local organic lesions fall into four categories:

1 *Nerve Block.*—Ulnar nerve block at the elbow to paralyze the vasomotor nerves of the little finger so that the consequent rise in temperature in this digit could be observed was utilized by Lewis (1929). Morton and Scott (1930) advocated blocking of peripheral nerves (ulnar, median, posterior tibial) as the simplest method of estimating the vasodilator response. They also reported the use of spinal anesthesia for the purpose of estimating the capacity for increased blood flow in the lower extremities Brill and Lawrence (1930) reported the use of spinal anesthesia for the same purpose White (1930) pointed out that the vasomotor nerves in the extremities may be blocked temporarily by paravertebral injection of procaine quite as effectively as by actual section of the sympathetic nerves. All of these methods afford a quantitative measure of the elevation of peripheral temperature which can be expected following sympathetic denervation. Blocking with procaine undoubtedly is the most accurate means available for studying vasomotor activity

2 *General Anesthesia*—Anesthesia induced by most of the general anesthetic agents commonly employed is accompanied by vasodilatation throughout the entire cutaneous area comparable to that produced in a limited area by procaine block of sympathetic ganglia or peripheral nerves. Under general anesthesia, the vasoconstrictor gradient in the extremities is abolished as soon as the anesthesia reaches a stage which produces moderate muscular relaxation The elevation of the skin temperature in the distal parts of the extremity, therefore, affords a reliable index of the vasodilator capacity In spite of its effectiveness as a method for the quantitative estimation of the capacity for peripheral vasodilatation, the common use of general anesthesia for this purpose is unwarranted since its induction and after effects are more disagreeable to the patient than are other methods

3. *Heating the Body.*—Lewis and Pickering (1931) described a method which involves heating of the body of the patient in a cabinet from which the head and arms protrude into the cooler atmosphere of the room (68° F.) Patients without arterial occlusion respond to this treatment by rapid warming of the hands to the normal vasodilatation level as soon as the body within the cabinet begins to perspire. Coller and Maddock (1932) induced vasodilatation by the use of heavy blankets and a rubber sheet Pickering (1932) has shown that vasodilatation occurs in the skin as soon as the

temperature of the blood is elevated 0.018° to 0.072° F. (0.01° to 0.04° C.) and that this response is mediated through the central heat regulating mechanism.

Gibbon and Landis (1932) described a method of increasing the temperature of the blood by having the patient sit with legs and forearms immersed in hot water (110° to 112° F.) while the extremity to be tested is exposed to the atmosphere of the room. In the absence of local arterial lesions dilatation of the cutaneous vessels becomes apparent in fifteen minutes and should be complete within thirty minutes.

These methods of heating the body and still others which have been reported are extremely simple and may be utilized with little inconvenience to the patient. The results usually are comparable to those of nerve blocking with procaine. In cases in which the response is not clean cut the patient may be tested again with procaine block.

4. *Foreign Protein Injection.*—The earliest practical method of differentiating limitation of circulation in the extremities due to vasospasm from that due to organic arterial occlusion was devised by Brown (1926). It involves the production of artificial fever by the intravenous injection of a foreign protein and measuring the circulatory response in the extremities during the fever reaction. This method, although effective, has quite generally fallen into disuse because the intense febrile reaction is extremely disagreeable to the patient and, in cases of advanced organic vascular disease, distinctly dangerous.

Raynaud's Disease.—The term Raynaud's disease has been loosely applied in the past to a wide variety of circulatory disorders. In order properly to limit this term, the Circulatory Clinic of the Massachusetts General Hospital has drawn up the following definition: "Raynaud's disease is a form of peripheral vascular disturbance caused by tonic contraction of the smaller arteries in the extremities without obvious pathological changes in their walls. It commonly involves symmetrical areas in the hands or feet causing excessive perspiration and circulatory stasis with periods of cyanosis or pallid asphyxia. The severe cases go on to dry gangrene of the phalanges. The spasm is intermittent and occurs on exposure to cold or emotional stimuli; it involves only the terminal arteries while the main vessels continue their normal pulsations. The disease most commonly occurs in young individuals with hyperirritable nervous constitutions."

According to Raynaud's original account, this disease arises as a vasomotor neurosis. Most of the more recent investigators support this opinion. After a prolonged period of resulting circulatory stasis secondary changes take place in and around the digital arterioles. On the basis of an extensive series of exceedingly interesting observations, Lewis (1929) concluded that the underlying cause of the circulatory disorder in Raynaud's disease is not vasoconstrictor hyperirritability but a local lesion involving the smooth muscle of the arterioles. According to his conception the digital arterioles themselves are hypersensitive to cold and respond to chilling by abnormal contraction. With this underlying hypersensitive mechanism, the normal variations in vasomotor tonus are sufficient to bring about all the circulatory changes observed in Raynaud's disease.

Following the publication by Lewis of his findings, Simpson, Brown and Adson (1930) undertook a further study of the factors underlying the cir-

culatory disturbances in Raynaud's disease. In early and relatively mild uncomplicated cases, according to their findings, the digital arteries and arterioles show no abnormal changes, but the abnormality lies wholly in the vasomotor nerves Complete sympathetic denervation by operation or anesthesia completely removes the symptoms in these cases In severe and complicated cases, they found abnormality both of the vasomotor nerves and the digital arterioles They interpreted the abnormality of the digital arterioles as a late effect of the disease In their experience, lumbar sympathectomy never failed to abolish the manifestations of the disease in the feet Cervicothoracic sympathectomy failed in some instances permanently to abolish all the circulatory manifestations of the disease in the hands This may be due in part to the changes in the digital arterioles but, in some of these cases, they also found evidence of the existence of some functional sympathetic fibers in the extremity following the operation

On the basis of the responses to local cooling of the digital vessels in relatively advanced cases of Raynaud's disease, Lewis (1936) concluded that vasomotor tonus is normal in these patients and that the peripheral spasm is due to increased reactivity of the musculature of the digital arterioles to cold According to his account, a typical localized vasospastic attack may be induced by cold stimulation applied at the base of a finger without causing a generalized reaction of the sympathetic nerves He also stated that complete blanching of the fingers cannot be brought about by vasoconstrictor reflex activity while the hand is at rest below the level of the heart Observations reported by certain other investigators, particularly Simpson, Brown and Adson (1930), do not corroborate the latter claim.

In a comparative study of the digital vascular pathology in warm handed individuals with that observed in various stages of Raynaud's disease, Lewis (1938) found that thickening of the intima occurs commonly in the former group after the age of fifty, and is no more marked in the earliest stages of the disease in the latter group in patients of comparable age The media exhibits no evidence of hyperplasia in the early stages. In more advanced stages of Raynaud's disease thrombotic obstruction of the digital arteries in various stages of organization is a common phenomenon In advanced stages, the capillaries commonly exhibit a characteristic pattern involving striking elongation, tortuosity and dilatation of the loops, particularly in the nail bed, in which stagnant erythrocytes become concentrated.

Lewis has interpreted the observation that spasm of the digital arterioles may be induced by local cooling after sympathetic denervation as supporting his contention that the reaction is due solely to a local fault in the digital vessels Certain other data fail to support this conclusion but indicate that such residual vasospasm may be explained more satisfactorily on the basis of increased sensitivity of the denervated arteriolar musculature to adrenin (Chapter V) This phenomenon is more striking in the hand than in the foot, due to the more complete degeneration of the postganglionic vasoconstrictor fibers after sympathetic denervation of the upper extremity, as the operation usually has been carried out. It is not without interest in this connection that Lewis (1938) also recognized preganglionic sympathectomy as more effective than ganglionectomy for the relief of vasospasm.

Lewis undoubtedly has made a notable contribution in pointing out that

local lesions of the digital arteries may play a significant role in the manifestations of Raynaud's disease even in relatively early cases. The existence of such lesions, particularly in advanced cases, has been amply verified. Most of the data available fail to support his conclusion that the local vascular lesions constitute a primary factor, but favor Raynaud's original conclusion that at the onset of the disease the recurrent vasospastic attacks are due to hyperreactivity of the vasoconstrictor nerves.

Among recent investigators who support the assumption that Raynaud's disease is primarily a local vascular disorder may be mentioned Hyndman and Wolkin (1942). They claim to have demonstrated that the disorder still exists objectively, as indicated by the observation that cold continues to cause color changes typical of Raynaud's disease in the hands following either sympathetic ganglionectomy or preganglionic sympathectomy. This objective response according to their account is diminished in mild cases but only in a degree which might be regarded as due to removal of the normal vasomotor tonus. It should be noted in this connection that they regard it necessary to remove only the second thoracic sympathetic trunk ganglion in order to effect complete sympathetic denervation of the upper extremity.

In a study of digital capillary blood pressure in patients with Raynaud's disease and scleroderma both before and after sympathetic denervation Fielma (1943) found that cessation of the blood flow through the capillary bed during vasospastic circulatory arrest induced by cold was caused by closure of the vessels proximal to the capillaries while the capillaries, venules and veins remained patent. In fingers with intact circulation the average capillary blood pressure was found to be 18.7 mm Hg in the arteriolar limb 22.1 mm Hg at the summit and 19 mm Hg in the venous limb. The gradient of fall in pressure through the capillaries usually was less than 3 mm Hg. In the fingers of a sympathectomized extremity the average capillary blood pressure was found to be 27.8 mm Hg in the arteriolar limb 25.2 mm Hg at the summit and 21.6 mm Hg in the venous limb. The gradient of fall in pressure through the capillaries was still small (6 to 7 mm Hg) but the greater pressure in the arteriolar limb indicated release of arteriolar tonus.

On the basis of Raynaud's theory of the etiology of this disease sympathetic denervation may be regarded as a rational therapeutic procedure. Nearly all who have reported the results obtained by this method of treatment agree that the milder cases and those in which the disease has not advanced to the stage of marked local pathologic changes in the vessels may be benefited by sympathectomy. Some investigators, including Boggan (1931), Gask and Ross (1931) and Hyndman and Wolkin (1942) who support the theory of Lewis that Raynaud's disease is primarily a local disease of the digital arteries advocate operation because paralysis of the vasoconstrictor nerves results in increased caliber of the denervated arteries. Local spasm which may take place following sympathetic denervation consequently, should be less damaging since the lumina of the vessels involved are larger.

The first essential in selecting patients for operation is a correct diagnosis. In patients over fifty years of age advanced arteriosclerosis should be ruled out by roentgen ray examination. Finally, regardless of the age of

the patient, the capacity for vasodilatation in the extremities should be determined by one of the preoperative tests outlined in the present chapter

On the basis of the results obtained in 83 sympathectomies in 54 patients with Raynaud's disease and other peripheral vascular disorders with spasticity and without spasticity, Shumacher (1943) concluded that sympathectomy yields excellent results in Raynaud's disease and other purely vasospastic circulatory deficiencies The extremities usually become warm and dry and the vasospastic attacks cease. Emotional stimulation no longer initiates attacks but in a small percentage of cases the extremities continue to cool abnormally on exposure to low temperature, probably due to local lesions of the peripheral vessels.

Scleroderma.—Scleroderma not infrequently is associated with Raynaud's disease. In certain cases in which this association existed, sympathectomy for the relief of Raynaud's disease was followed by improvement in the condition of the skin In other cases, sympathectomy carried out in the treatment of scleroderma has been beneficial in some but resulted in no marked improvement in others. Adson, O'Leary and Brown (1930) reported excellent results particularly in early cases in which little fibrosis and atrophy had taken place. In the more advanced cases the pain was greatly alleviated and the vasomotor crises subsided The results of sympathectomy reported by Leriche, Jung and de Bakey (1937) are less striking In their experience, sympathectomy in a relatively small number of cases was followed by improvement in the condition of the skin in varying degree in approximately two-thirds of the patients The results of parathyroidectomy in another series of cases, as reported by these investigators, were somewhat better Since patients with scleroderma exhibit disturbances in calcium metabolism and the calcium content of the skin is increased (Kaether and Schaefer, 1940), sympathectomy combined with parathyroidectomy might be expected to yield more satisfactory results than either operation alone, particularly in cases in which there is a marked element of vasospasm.

The etiology of scleroderma as yet is not fully known Thickening of the musculature of the peripheral arterioles and hypertonus of the peripheral vessels have been reported repeatedly Since scleroderma is frequently associated with Raynaud's disease and other peripheral vascular disorders, evaluation of the clinical syndrome and the results of diagnostic tests must be made in the light of this fact Both peripheral and central autonomic nerve lesions have been reported particularly in cases in which scleroderma is obviously associated with Raynaud's disease (Sunder-Plassmann and Jaeger, 1940). Hoff (1941) reported a case of scleroderma associated with diabetes caused by a tumor in the hypothalamic region in which both disease processes subsided following surgical removal of the tumor. In another case reported by Hoff, administration of ergotamine over a period of two years resulted in typical scleroderma which cleared up after the medication was discontinued. Other evidence that autonomic dysfunction is a factor in the etiology of scleroderma is not wanting For example, the fluctuations in the flow of blood in the skin corresponding to fluctuations in the external temperature and the spontaneous improvement in the condition of the skin frequently observed following febrile reactions afford comfirmatory evidence of exaggerated vasomotor tonus Other factors related to endocrine dysfunction undoubtedly are present in most

cases and may play a major role. The general application of sympathectomy in the treatment of this disease, therefore, is unwarranted.

Thrombo-angiitis Obliterans. — Thrombo-angiitis obliterans not infrequently exhibits a large factor of vasospasm; consequently, it may be impossible in its early stages to differentiate it from a primary vasomotor disorder. According to Brown *et al.* (1928), it "is fundamentally a chronic inflammatory condition of the vessels accompanied by proliferation of the intima and resulting in thrombosis with organization and canalization of the clot, fibrosis of the adventitia and an attempt on the part of the vasa vasorum and other vascular channels to establish a collateral circulation. At times acute inflammation is superimposed on the chronic process. The nerves are involved apparently by virtue of their relationship to the vessels and by ischemia in the distal portions."

In cases in which preoperative tests have indicated satisfactory capacity for increased circulation, sympathetic denervation has resulted in benefit even in the presence of organic occlusion in some degree. Brown and his associates have emphasized the importance of selecting patients with this disease for operation on the basis of their capacity for vasodilatation as indicated by diagnostic tests. During their earlier experience with sympathectomy in the treatment of thrombo-angiitis obliterans approximately one patient in seven was selected for this operation. Later the ratio has been increased to one in three (Adson and Brown, 1932). On the basis of their experience they concluded that sympathectomy is indicated in all cases in which induced fever results in a rise in skin temperature of the digits twice as great as the rise in mouth temperature, or nerve block results in a rise in skin temperature of the digits of at least 3° C.

Beneficial results of sympathectomy in some cases have been reported by various investigators, including Telford and Stopford (1933) and Hotham and Swift (1933). In summing up the results of 45 operations Telford (1934) regarded them as satisfactory in approximately 50 per cent of the cases, while an additional 25 per cent showed distinct improvement. Smithwick and White (1930, 1935) have employed sympathectomy in combination with other forms of treatment, such as minor amputations of digits and crushing of peripheral nerves, with satisfactory results in many cases. They have emphasized the value of the accessory treatment. In cases in which pulsations cannot be palpated in the main arteries, including the femoral, in their experience, sympathectomy usually is of no avail, particularly in the presence of ulceration, infection or gangrene.

In evaluating sympathectomy in the treatment of thrombo-angiitis obliterans, the progressive and disabling character of this disease must be kept in mind. Arrest of the disease process is not to be expected, but in selected cases sympathectomy may be regarded as a warranted conservative measure to avoid or postpone amputation or to permit it to be carried out more distally.

Arteriosclerosis. — Arteriosclerosis may in certain cases be associated with sufficient vasospasm to warrant interruption of the vasoconstrictor nerves to the extremities. Criteria for the selection of arteriosclerotic patients suitable for operation and a resumé of the results obtained in a limited number of patients subjected to lumbar sympathectomy have been presented by Atlas (1941). The results reported are highly encouraging, but it must be pointed out that the patients were carefully selected and the

group included only cases in which preoperative tests indicated a healthy collateral arterial circulation and a flexible arteriolar bed in which muscular tonus was maintained at a level so high that conservative therapy was of no avail.

In a later communication, Atlas (1942) pointed out that surface temperature determinations do not, in all arteriosclerotic patients, afford a reliable criterion for evaluating the nutritive efficiency of the circulation through the feet, since surface temperature apparently is controlled by the volume rate of blood flow through the arteriovenous anastomoses. In the presence of advanced arteriosclerosis in the feet, sympathetic denervation may actually produce disastrous results because, in the absence of an effective collateral circulation, elimination of the vasomotor tonus permits so much blood to flow through the arteriovenous shunts that the volume flow through the capillary bed is insufficient to supply adequate nutrition and oxygen to the tissues. In his experience, sympathetic denervation has been followed by gangrene in the foot in certain cases.

In the presence of extensive arteriosclerosis, according to Atlas, evaluation of the capacity of the arteriolar and capillary bed in the foot to dilate requires more than a single test. Constant and severe pain in the foot, extreme pallor on elevation, cyanosis and reddening on dependency, atrophy of the skin and subcutaneous tissue with loss of elasticity, significantly delayed filling and emptying of the dorsal venous arch, and intensification of the pain and cyanosis on immersion of the foot in warm water indicate advanced involvement of the collateral circulation in the arteriosclerotic process This combination definitely contraindicates sympathectomy Its absence indicates an open and healthy collateral circulation. Only patients in which it is absent may be regarded as suitable for sympathectomy.

Chronic Ulceration of Extremities.—Deep thrombophlebitis, varicose veins or bouts of cellulitis, particularly in the lower third of the leg, may be followed by chronic indolent ulceration. This condition may be accompanied by vasospasm due to hyperactivity of the vasomotor nerves or induced reflexly by the peripheral irritation, particularly in cases in which pain is a significant factor. Improvement following sympathectomy has been reported particularly in cases in which preoperative tests revealed a large element of vasospasm (Craig and Brown, 1930). White and Smithwick (1941) reported beneficial results of sympathectomy in the treatment of certain cases of thrombosis of the brachial artery with chronically impaired circulation Beneficial results of sympathectomy in the healing of both infected and uninfected wounds in the extremities also has been reported (Rieder, 1927)

The production of reflex vasospasm in the extremities elicited by peripheral vascular irritation has been demonstrated experimentally by Stricker and Orban (1930), Reichert (1932), Oughterson, Harvey and Richter (1932), Theis (1933), de Bakey, Burch and Ochsner (1939) and others. In the experiments of de Bakey *et al.*, reflex spasm of peripheral arteries and veins elicited by chemical irritation of a venous segment resulted in marked diminution of peripheral pulsations and a rise in venous pressure, which were abolished by interruption of the sympathetic nerves. Ochsner and de Bakey (1939, 1940) have emphasized the importance of this reflex mechanism in the production of the clinical manifestatic

thrombophlebitis, thus indicating the rationality of sympathectomy or nerve blocking in the management of these cases. The results of early and repeated blocking of the lumbar sympathetic ganglia with procaine as summarized by Smithwick (1941), include improvement in circulation, reduction of swelling and prompt relief of pain. Untoward sequelae such as swelling, superficial varices or ulceration were not observed.

In cases of acute interruption of the flow of blood in major arteries due to acute embolism, ligation or laceration, prompt elimination of vasospasm by paravertebral nerve blocking or sympathectomy may materially reduce the incidence of gangrene. In the management of these cases and certain other vascular lesions, supplementary treatment such as intermittent venous occlusion (Collens and Wilensky, 1939), passive vascular exercise (Landis and Gibbon, 1933; Herrman and Reid, 1933; Herrman, 1936) and the oscillating bed (Sanders, 1936) may be used to hasten the development of collateral circulation.

Erythromelalgia. — Erythromelalgia is a condition characterized by redness and burning pain in the extremities. The patient may be wholly incapacitated and unable to tolerate the slightest pressure or covering of the feet. Attacks may be brought on by the dependent position of the feet, heat or exercise. The vessels of the feet are greatly dilated and arterial pulsations are present. Since active vasodilatation, like vasoconstriction, is mediated by the sympathetic nerves, the capacity for active vasodilatation as well as for vasoconstriction is abolished in a sympathectomized extremity; consequently, sympathetic denervation may be expected to yield beneficial results in cases of erythromelalgia. Proceeding on this assumption, Telford and Simmons (1940) have carried out lumbar sympathetic ganglionectomy in a few cases, in all of which the circulation in the feet returned to normal and the pain subsided.

Essential Hypertension. — The causes of essential hypertension as yet are unknown but certain etiological factors have been recognized. Among these may be mentioned primary vascular disease, vasomotor dysfunction, endocrine activity and vasospastic humoral substances, all of which may be effective in varying degrees. The neurogenic factors may be modified or in part eliminated by extensive sympathetic denervation. This may be expected to afford some measure of relief in cases in which there is a large element of vasospasm. If the effect of the renal pressor hormone is exerted mainly through the central vasomotor control mechanism, as the experimental data advanced by Dock, Shidler and Moy (1942) seem to indicate, this effect also may be eliminated in a large measure. In the presence of occlusive vascular disease, sympathetic denervation can effect reduction in the blood pressure only to the extent permitted by the capacity for dilatation still retained by the blood vessels.

Various operative procedures have been employed in attempts to relieve hypertension. Those which have yielded the most satisfactory clinical results involve extensive splanchnic sympathetic denervation. Such operations insure not only removal of the vasoconstrictor innervation in extensive areas but also inhibition of adrenin secretion, thus minimizing the effect of sensitization of the denervated vessels to this hormone.

The flow of blood through the kidneys, the limitation of which has been recognized as an important factor in the experimental production of hypertension in animals (Goldblatt, 1940), is not materially altered by splanchnic

sympathetic denervation in hypertensive patients (Corcoran and Page, 1941, Selzer and Friedman, 1941; Findley, Clinton and Edwards, 1942). The reduction in blood pressure observed in these patients following splanchnic denervation probably is due mainly to the increased capacity of the vascular bed in the sympathectomized area.

Unilateral splanchnic resection for the relief of hypertension was reported by Pieri as early as 1932 Adson and Brown (1934) reported an operative technic involving laminectomy and section of anterior spinal nerve roots. Craig (1934) reported resection of the splanchnic nerves by a subdiaphragmatic approach. Peet (1935) reported splanchnicectomy by a supradiaphragmatic approach. Crile (1937, 1938) reported celiac ganglionectomy. These operative procedures have been variously modified by their authors and other surgeons The literature bearing on the surgical treatment of hypertension has become too voluminous to permit of a complete review in this connection. Among the more significant later reports may be mentioned those of Freyberg and Peet (1937), Adson and Allen (1936), Allen and Adson (1939), Peet, Woods and Braden (1940) and Smithwick (1940) The operative procedures, as most commonly carried out at present involve splanchnic resection combined with extirpation of several segments of the sympathetic trunks in the lower thoracic or the upper lumbar region or both, the common aim being extensive vascular denervation Splanchnic nerve resection and sympathetic trunk extirpation by which such extensive vascular denervation may be achieved are suggested in Figure 91

The report of Peet, Woods and Braden (1940) summarizes the results observed in 350 consecutive cases operated upon by Peet during a period of seven years. The operative procedure employed was essentially the same in all cases and included bilateral supradiaphragmatic splanchnicectomy and lower thoracic sympathetic ganglionectomy. According to their report, 86 6 per cent of the patients experienced postoperative relief of the major symptoms, especially headache, 81.3 per cent showed relief of incapacitation or improvement in this respect and 51 4 per cent showed significant reduction in blood pressure The most favorable results were obtained in patients under thirty years of age In older patients age appeared to be but a minor factor in the results of the operation. On the basis of the results obtained, which in many cases have continued over a period of years, they concluded that this form of surgical treatment offers a better prognosis in cases of severe hypertension than therapy of any other kind as yet reported.

In a discussion of 300 cases treated by bilateral subdiaphragmatic splanchnicectomy and extirpation of the two upper lumbar sympathetic trunk ganglia, Allen and Adson (1940) listed the results in 224 patients, with respect to reduction in blood pressure, as good in 13 per cent, fair in 18 per cent, temporary in 39 per cent and poor in 30 per cent. In their experience, clinical symptoms invariably disappeared with reduction in blood pressure and in some instances the patient continued without clinical symptoms even though there was a gradual return of increased blood pressure. They emphasized the importance of early operative treatment, before the renal and cardiovascular tissues have suffered irreparable damage

In discussing the results of splanchicectomy by the supradiaphragmatic and the subdiaphragmatic approaches, a combination of these two pro-

cedures, and splanchnicectomy combined with bilateral extirpation of the upper two or three lumbar sympathetic trunk ganglia, White and Smithwick[1] (1941) have pointed out that the reduction in blood pressure becomes more significant as the splanchnic denervation becomes more complete, particularly when the patient assumes the upright position. In some of their cases which showed no appreciable reduction in blood pressure following splanchnicectomy alone by the supradiaphragmatic approach, a significant reduction was maintained even in the horizontal position after additional bilateral extirpation of the lumbar sympathetic trunk ganglia. This operation obviously effects sympathetic denervation of the lower extremities as well as of the splanchnic area.

In the light of all the data available, it is apparent that in certain hypertensive patients the blood pressure can be significantly and permanently lowered by splanchnicectomy. In some of these patients a cure may be effected. In others the span of life may be increased. Patients in whom the blood pressure is significantly lowered almost invariably experience improvement in symptoms and show favorable changes in renal, cardiac, ocular and cerebral manifestations if present before operation. Most of the patients subjected to splanchnicectomy have shown no significant reduction in blood pressure but many of these have obtained symptomatic relief in a high degree and have been able to return to work. Some have experienced no improvement of any kind.

Hypertensive patients obviously should be selected for operation with great care. According to Allen and Adson (1940), the results of operation can be predicted with reasonable certainty on the basis of the response of the blood pressure to rest and sleep and the induction of sedation by ingestion of sodium amytal or the intravenous injection of pentothal sodium. If the blood pressure fails to drop to the normal level on sedation, renal function is impaired, or there is evidence of advanced vascular changes such as cerebral accidents and particularly impaired cardiac function, unfavorable results may be anticipated.

Other Conditions Improved by Increased Circulation.—*Anterior Poliomyelitis.*—In view of the manifestations of inadequate circulation in extremities partially or completely paralyzed as a result of anterior poliomyelitis, benefit to the patient might be expected from sympathetic denervation of the extremity due to the increased circulation insured by interruption of the vasomotor nerves. Harris (1930) and Harris and McDonald (1936) reported favorable results of lumbar sympathectomy in children with residual paralysis following anterior poliomyelitis. In their series of 46 sympathectomies, hyperemia was maintained in 32. In 26 of these the rate of growth was accelerated on the operated side. In a limited series reported by Telford (1934), he observed elevation of skin temperature in the sympathectomized extremities and decreased proneness to chilblains and chronic ulceration. White and Smithwick (1941) reported elevation of the skin temperature and acceleration in the rate of growth in a partially paralyzed limb of a child following lumbar sympathectomy.

The results of operation reported by various surgeons appear to indicate sympathectomy following poliomyelitis, particularly in children, if the residual motor function is sufficient to permit of some use of the limb. If the limb is completely paralyzed, lasting improvement in the circulation cannot be obtained, and sympathectomy is contraindicated.

Healing of Fractures.—Acceleration of bony union following sympathectomy, in cases in which union was delayed following fractures of bones of the extremities, has been reported. The results of experimental studies bearing on this point are not encouraging. In experiments reported by McMaster and Roome (1932) in which equal fragments (approximately 1.5 mm. in length) of the fibulæ were removed in dogs which had been subjected to unilateral lumbar sympathectomy, the healing process was completed earlier in the normally innervated leg than in the sympathectomized one. Key and Moore (1933), who tested the effect of sympathectomy on the healing rate of bone and articular cartilage in cats, found no difference in the rate of repair on the sympathectomized and the control sides. Zollinger (1933) reported experiments carried out on dogs in which the effects of sympathectomy both preceding and following fractures of the fibulæ were observed. In all but 2 of 17 experiments regeneration of the bone went on more rapidly on the sympathectomized than on the normally innervated side regardless of whether sympathetic denervation preceded or followed the fracture. This acceleration was not regarded as great enough to warrant the application of sympathectomy as a clinical measure designed to hasten bony union in cases of fracture.

In a study of the effect of sympathectomy on the blood supply of bone in the rat, Zinn and Griffith (1941) found that the supply to the tibia was actually decreased five days after lumbar sympathectomy, probably due to disproportionately greater dilatation of the vessels in the soft tissues than in the bone. Increased vascularity of the periosteum at the site of a fracture and the resulting scar tissue undoubtedly is a factor in the healing process. This apparently is not materially increased following sympathetic denervation, due to the compact character of the tissues in question. Injection of the arteries in specimens of old ununited fractures has shown that few large vessels actually penetrate through the dense scar tissue which surrounds the fracture.

Cardiac Disease.—Angina Pectoris.—Sympathectomy in the treatment of angina pectoris was carried out by Jonnesco as early as 1916. On the assumption that impulses of pain are conducted from the heart through visceral afferent spinal nerve components associated with the sympathetic cardiac nerves, the correctness of which has since been amply demonstrated, he removed the middle and inferior cervical and first thoracic sympathetic trunk ganglia in order to interrupt the afferent conduction pathways from the heart to the spinal cord. Extirpation of these ganglia on the left side only sufficed, in his first case, to relieve the symptoms of angina pectoris in a most striking manner. In later operations he removed the superior cervical as well as the middle and inferior cervical and first thoracic sympathetic trunk ganglia. Although the results in Jonnesco's early cases were most satisfactory, they did not stimulate widespread interest in the surgical treatment of angina pectoris because his operation was regarded as too drastic.

Coffey and Brown (1923) reported 5 cases in which extirpation of the left superior cervical sympathetic ganglion alone or section of the superior cervical cardiac nerve and the sympathetic trunk below the superior cervical ganglion sufficed to ameliorate the painful seizures of angina pectoris. These results seemed to demonstrate the feasibility of surgical intervention in cases of angina pectoris without extensive operation and

without interrupting the afferent conduction pathways from the heart They also stimulated interest in the surgical treatment of angina pectoris along these new and simpler lines

During the following decade various surgeons carried out more or less extensive cervical sympathetic extirpation in the treatment of angina pectoris with benefit to the patient in some cases and without benefit to the patient in others (Cutler, 1927, Hesse, 1927) In a review of cases reported in the literature, Leriche and Fontaine (1932) found that cervic sympathectomy without removal of the inferior cervical ganglion produce satisfactory results in 58 per cent of 16 cases Of the cases reviewed i which the inferior cervical ganglion also was removed, good results we reported in 70 per cent

On the basis of our present knowledge of the innervation of the hea and coronary vessels (see Chapter VII) the beneficial results of unilater cervical sympathectomy which have been reported cannot be explaine satisfactorily Section of the left superior cervical cardiac nerve or extirp tion of the superior cervical sympathetic ganglion interrupts but a mino portion of the sympathetic fibers to the heart and coronary vessels an none of the afferents Extirpation of the entire cervical portion of th sympathetic trunk including the inferior cervical or stellate ganglion o extirpation of the inferior cervical or stellate ganglion alone interrupts larger portion of the sympathetic innervation and the afferent spinal nerv components associated with the middle and inferior cervical sympathet cardiac nerves but leaves a large percentage of the cardiac accelerator fibe and afferent spinal nerve components associated with them in the thorac cardiac nerves intact In some instances, interruption of only the cervic sympathetic cardiac nerves on the left side may be sufficient to relie coronary vasoconstrictor tonus on that side and to interrupt enough pai conducting fibers to relieve pain of cardiac origin In other instanc cervical sympathectomy alone is inadequate to relieve the pain of angin attacks as indicated by the reported failures of such operations

White (1930) demonstrated by paravertebral injections of novocain and procaine, that the afferent fibers which conduct impulses of pain fro the heart in cases of angina pectoris enter the spinal cord via the com municating rami in the upper thoracic segments, including the fourth H therefore, regarded the upper thoracic segments of the sympathetic trun as the logical points of attack in the treatment of angina pectoris an recommended extirpation of the upper two or three thoracic sympatheti trunk ganglia in order to interrupt the major portion of the pain-conductin fibers If the pain radiates to the left as it does in most cases the operatio should be carried out on the left side If it radiates to the right side onl as it does in some cases, the operation should be carried out on the righ side White (1933) and Braeucker (1933) reported limited series of case in which extirpation of the inferior cervical and the upper two thorac sympathetic trunk ganglia resulted in satisfactory relief of anginal attack

This point of view, which emphasizes interruption of the pain conductio pathways as the primary aim in the surgical treatment of angina pector has now been quite generally adopted Interruption of the sympatheti innervation of the coronary vessels undoubtedly is a significant factor i many cases (Raney, 1939) since, according to the best available evidence, the sympathetic cardiac nerves include the coronary constrictor fibers (see

Chapter VII). Unilateral section of the cardiac accelerator nerves, furthermore, results in no apparent damage to the heart or appreciable retardation of the cardiac rhythm. The operation, therefore, can be carried out without undue danger to the patient It has been carried out successfully even in patients who had suffered recent coronary infarction or threatened cardiac failure (White and Smithwick, 1941).

Extensive interruption of the pain conduction pathways in the treatment of angina pectoris has been regarded as dangerous by some on the assumption that in the absence of pain there would be no warning of an impending attack. This assumption is not supported by the result of studies carried out on patients following such treatment. In an extensive series of patients in whom all sensation of pain of cardiac origin had been removed, White and Smithwick (1941) found that anginal attacks always were recognized by the patient, due to a sense of thoracic depression, palpitation, flushing or shortness of breath They regard surgical denervation as the method of choice for the relief of severe cardiac pain in patients who are reasonably good surgical risks

Patients with severe cardiac pain who cannot safely be submitted to surgical treatment may be benefited by blocking the sympathetic nerves by paravertebral injection of procaine followed by alcohol. Employment of this method has been reported by various surgeons, including Mandl (1925), Swetlow (1926), Bernard (1937), Ochsner and de Bakey (1937), Jessen (1938), White (1940) and others Although complications such as intercostal irritation and neuritis occur not uncommonly, this method of treatment involves a minimal risk and, if successfully applied, may be as effective as sympathetic ganglionectomy. If the alcohol is placed with sufficient accuracy to insure destruction of the sympathetic ganglia, the results are no less permanent than those of surgical intervention.

Cardiac Arrhythmias —Various alterations of the cardiac rhythm undoubtedly are associated with autonomic dysfunction. In experiments reported by Beattie, Brow and Long (1930), asystoles under light chloroform anesthesia were abolished by section of the cardiac accelerator nerves. A neurogenic factor in the causation of various ectopic cardiac rhythms is indicated by the fact that they are promoted by adrenin and abnormal excitation of the sympathetic cardiac nerves (Nahum and Hoff, 1935) Recurrent bouts of paroxysmal tachycardia and fibrillation also have been abolished by bilateral sympathectomy (Leriche and Fontaine, 1929, Langeron, Desbonnets and Delvallez, 1935; Coleman and Bennett, 1938). On theoretical grounds it may be assumed that interruption of the accelerator fibers on the right side is of major importance in these cases, since the pace-making mechanism is located in the walls of the right atrium.

CHAPTER XXIV

AUTONOMIC NEUROSURGERY (Continued)

OTHER DISEASES WITH AUTONOMIC FACTORS VISCERAL PAIN AND PAIN IN EXTREMITIES

Arthritis.—Not infrequently arthritis is associated with exaggerated vasomotor tonus in the extremities and other evidence of heightened sympathetic activity such as perspiration in the presence of subnormal skin temperature. These conditions may be secondary to the inflammation around the joints but the arthritic disease undoubtedly is aggravated by the limitation of the blood supply to the joint capsules and adjacent tissue due to the exaggerated vasoconstrictor tonus. The rationality of sympathectomy in the treatment of chronic arthritis therefore is indicated particularly in cases in which it is associated with marked vasoconstriction.

Rowntree and Brown (1927) reported a single case of polyarthritis in which the results of sympathectomy were very striking. The patient, a woman thirty-four years of age, had failed to respond to medical treatment for six years. Her limbs were badly crippled, hands and feet were cold and moist, with trophic changes in the skin and nails, the interphalangeal joints were all enlarged and the ankles, wrists, elbows and shoulders showed considerable limitation of motion. Pain was marked over the metatarsal arch and in the wrists, elbows and knees. Following bilateral extirpation of the second, third and fourth lumbar sympathetic ganglia the feet became warm, dry and pink, the skin desquamated and the trophic changes receded. The pain disappeared entirely in the lower extremities and the patient was able to walk a distance of 1½ to 2 miles before leaving the hospital. All this is in striking contrast to the condition of the upper extremities which remained cold, clammy and painful. The surface temperature of the hands was found to be 9° C. lower than the surface temperature of the feet following operation. A later operation involving bilateral extirpation of the inferior cervical and first and second thoracic sympathetic ganglia produced results in the upper extremities similar to those produced by lumbar sympathectomy in the lower extremities (Rowntree 1929).

Encouraged by these results Rowntree advised sympathectomy in other cases of arthritis which failed to respond to medical treatment. In a review of 17 cases Rowntree, Adson and Hench (1930) pointed out that the best results were obtained in cases of arthritis of the periarticular type associated with neurocirculatory alterations. According to their account the operation alleviates the pain, relieves the excessive sweating and coldness of the extremities and supplies definite restorative influences to combat the trophic changes so that in many cases function is restored to a considerable degree. The most striking results were observed in the hands and feet. The knee- and elbow-joints responded less rapidly and the effect of the operation on the hip- and shoulder-joints was considerably retarded and not very marked. When osseous changes or ankylosis were present the results were less encouraging but even in some of these cases the pain was greatly alleviated.

Favorable results of sympathectomy in the treatment of polyarthritis have been reported by certain other surgeons, particularly Flothow (1930) and Young (1936) In the experience of not a few, the results of this form of treatment have been disappointing In many cases circulation in the sympathectomized extremities has been improved, the skin temperature elevated and perspiration abolished. In some, pain was alleviated in a measure, at least temporarily, others experienced no appreciable change with regard to pain. In certain patients, as reported by White and Smithwick (1941), the disease advanced more rapidly in the sympathectomized extremity than in the normally innervated ones.

In view of all the data available, the general application of sympathectomy in the treatment of chronic polyarthritis is unwarranted. This form of treatment undoubtedly is indicated in certain cases in which the superimposed exaggerated vasoconstrictor and sudomotor activity cause serious discomfort, but the suitability of patients for operation cannot be determined on this basis alone

Favorable results of sympathectomy in the treatment of traumatic arthritis (post-traumatic painful osteoporosis) have been reported by Fontaine and Hermann (1933). In some of their cases periarterial sympathectomy proved to be sufficient. White and Smithwick (1941) reported satisfactory results in a limited number of cases treated by paravertebral nerve blocking. They recommend this form of treatment in most cases, reserving sympathetic ganglionectomy for those cases in which more conservative methods have failed. The effectiveness of sympathetic denervation in the treatment of osteoporosis is significant since it is an incapacitating syndrome which is highly resistant to ordinary orthopedic measures.

Hyperhydrosis.—Hyperhydrosis of nervous origin usually is most marked on the palmar and plantar surfaces and the fingers and toes, and not infrequently is limited to the hands and feet. It usually is accompanied by vasospasm in some degree, so that the wet extremities frequently are cold and at times cyanotic The common clinical observation that secretory activity of the sweat glands is abolished in the affected area following interruption of the sympathetic nerves demonstrates the rationality of sympathectomy in the treatment of hyperhydrosis. Obviously, such drastic treatment should be considered only in cases in which sweating is extreme and incapacitating.

Among the earlier reports of sympathectomy in the treatment of hyperhydrosis are those of Kotzareff (1920), Braeucker (1928), Hesse (1930) and Pieri (1932). This method of treatment also has been advocated by Adson (1934), Adson, Craig and Brown (1935), List and Peet (1938) and others. The results reported have been consistently satisfactory. Nerve blocking by means of paravertebral infiltration of alcohol has been reported by White and Smithwick (1941) but they regard surgical sympathetic denervation as preferable, except in exceptional cases, since its effects are certain and the operative risk is almost nil in this group of patients, most of whom are young and otherwise in good health. Preganglionic section offers no advantage over ganglionectomy in this condition since the sudomotor fibers are cholinergic and sensitization of the sweat glands to hormonal stimulation does not take place following degeneration of the postganglionic fibers.

Carotid Sinus Syndrome.—The carotid sinus mechanism, which plays a significant role in the normal regulation of circulation and respiration (see Chapters VIII and IX), not infrequently becomes hyperirritable giving rise to a characteristic syndrome. In its fully developed form this syndrome includes recurrent attacks of syncope and is easily recognized. Exaggerated carotid sinus reflexes of three types have been described: (1) asystole or sudden retardation of the cardiac rhythm with or without marked reduction in arterial blood pressure, (2) pronounced decrease in blood pressure without marked retardation of the cardiac rhythm, (3) alterations in the cerebral circulation resulting in fainting and at times convulsions without marked change in the cardiac rhythm or blood pressure. The abnormal reflex response may be entirely unilateral or much more pronounced on one side than on the other. As pointed out by Weiss and Baker (1933), digital pressure on the hypersensitive carotid sinus may induce symptoms which are identical with those of spontaneous attacks.

Hyperactivity of the carotid sinus reflex mechanism may induce abnormal reactions of the intracardiac conduction system including complete heart block, temporary asystoles of the ventricles with continued contractions of the atria, ventricular extrasystoles, alterations in the form of the T-wave, and complete inversion of the electrical cardiac axis. Carotid sinus irritability may be increased by light spinal anesthesia, digitalis, etc. Manipulation of the hyperirritable carotid sinus or stimulation of the carotid sinus nerve during operations in the cervical region may result in alarming symptoms or even fatal collapse. Preoperative tests of the reflex excitability of the carotid sinus mechanism therefore should be carried out (Rovenstine and Cullen, 1939). In the presence of carotid sinus hyperirritability or when the field of operation is adjacent to the carotid sinus, the use of anesthetics which, like ether, tend to depress this mechanism are more advantageous than the use of those which, like spinal, tend to increase its reactivity.

Asystole or reflex slowing of the heart due to carotid sinus stimulation may be abolished by atropine, since the reflex response is mediated through parasympathetic nerves. A marked decrease in blood pressure may in some instances be relieved by adrenin or ephedrine, since these agents act not only to accelerate the cardiac rhythm but also to increase vascular tonus. Abolition of the primary attacks of syncope and convulsions may require complete blocking of the carotid sinus reflex mechanisms. This can be accomplished by infiltration of the tissues around the carotid sheath with procaine or resection of the carotid sinus nerve. Surgical denervation of the carotid sinus commonly abolishes all symptoms of reflex activity of the carotid sinus mechanism. Favorable results of carotid sinus denervation in the treatment of recurrent syncope and convulsions have been reported by various investigators including Weiss, Capp, Ferris and Munro (1936), Freedberg and Sloan (1937), Capps and de Takats (1938), Craig and Smith (1939), Romano, Stead and Taylor (1940), White and Smithwick (1941) and others.

Epilepsy.—A possible role of the carotid sinus and cardio-aortic nerves in epileptic seizures has been suggested by various investigators. Section of the carotid sinus nerves and partial section of the cardio-aortic nerves in the treatment of epilepsy has been reported by Danielopolu and Marcu (1928). On the experimental side these investigators (1932) reported that

clonic and convulsive movements induced by application of a strychnine solution to the motor cortex in dogs may be modified by stimulation or section of the cardio-aortic or carotid sinus nerves. When clonic or convulsive movements were apparent, stimulation of the central end of the severed vagus nerve or increased pressure on the carotid sinus resulted in their exaggeration In animals with the vagi intact, increasing blood pressure in the aorta, while the common carotid arteries were ligated, had but slight effect on the clonic movements, showing that the effects noted above were brought about reflexly, although increased pressure in the cerebral vessels may have played a minor rôle.

On the basis of these experimental results and the clinical data available, Danielopolu and Marcu advanced the opinion that if all the fibers of the carotid sinus and cardio-aortic nerves could be interrupted epileptic seizures might be abolished at least in some cases Section of all these nerves obviously would be fraught with danger, since the control of the cardiac rhythm and the blood pressure would be impaired. In animal experiments reported by Greiwe (1932), death usually followed section of both carotid sinus and cardio-aortic nerves within twenty-four hours. Of the few animals which survived this procedure, some which were kept alive for six months by frequent blood letting, exhibited extremely high blood pressure during the entire period and developed extensive and intensive arteriosclerosis These findings fail to support the assumption that section of either the carotid sinus or cardio-aortic nerves or both is a rational procedure in the treatment of epilepsy.

The hypothesis that cerebral vasoconstriction is a causative factor in epileptic seizures is supported by both experimental and clinical data (see Chapter XXI). On the basis of this assumption, cervical sympathectomy has been carried out in the treatment of epilepsy (Alexander, 1889; Jonnesco, 1896, and others) without marked success Since superior cervical sympathectomy does not interrupt all the sympathetic fibers which enter the cranial cavity along the vertebral arteries, Mixter and White, as reported by White and Smithwick (1941), carried out bilateral cervicothoracic sympathectomy in a series of patients suffering from frequent and severe epileptic seizures in order to effect complete sympathetic denervation of the cerebral vessels The results obtained in 3 of 17 cases appeared to be encouraging at first but the final outcome has been disappointing. These investigators have expressed the opinion that sympathetic denervation of the brain in epileptic patients has no significant effect on the convulsive state.

Spastic Paralysis.—The application of sympathetic ganglionectomy and ramisection in the treatment of spasticity of muscles of the extremities was advocated by Royle (1924) and Hunter (1924) on the assumption that the plastic component of the tonus of skeletal muscles is mediated through the sympathetic nerves and that this component may become exaggerated, in the presence of impairment of the voluntary nervous mechanism, resulting in spasticity If this assumption were correct, sympathetic denervation of a spastic extremity ought to relieve the spasticity and give the impaired voluntary nervous mechanism, if not completely destroyed, a chance with the aid of passive manipulation and other means of reeducation, to regain control of the muscles. The anatomic and physiologic data outlined in Chapter XVII fail to indicate a significant influence of the

sympathetic nerves in the tonus of skeletal muscles. The assumption on which Royle and Hunter proceeded, therefore, is not well founded. It should be pointed out that Royle did not advocate sympathectomy as a cure for spastic paralysis but maintained that "it merely removes a factor which has been interfering with the normal physical education of the individual and the essential treatment of spastic paralysis is education of the central nervous system."

The results of sympathectomy in Royle's early cases of spastic paraplegia, as set forth in his reports, were highly encouraging. Certain other surgeons also reported beneficial results in some cases. For example, Carrell (1926) who carried out sympathetic ramisection in 35 cases stated: "Improvement in function has not been marked, but in 15 cases the gait was improved to the extent of more ease in flexing and bending the knee and walking with less rigidity." In the hands of certain other surgeons, notably Kanavel, Pollock and Davis (1925), sympathetic ganglionectomy and ramisection, in cases of spasticity due to a variety of causes, resulted in no appreciable benefit to the patients. On the basis of the results obtained by sympathectomy in 10 cases treated in the New York Orthopedic Dispensary and Hospital, Von Lackum (1929) concluded that this operation "offers the most effective means of relief in many cases of spastic paralysis in children." According to his report, nearly every patient showed decreased spasticity in the affected extremity while at rest. Approximately two-thirds of the patients showed a striking reduction in rigidity following sympathectomy, both while active and at rest. The clinical results obtained in the lower extremities were described as excellent in approximately 20 per cent and as good in over 10 per cent of the cases. Certain patients, particularly children with marked mental deficiency, were not materially benefited by the operation. The results obtained in the upper extremities in a limited number of cases were less favorable than those obtained in the lower extremities.

In spite of much adverse criticism, Royle (1930), after having observed the results of sympathectomy in a large number of cases of spasticity due to various causes, still remained an ardent advocate of this procedure. On the other hand, Symonds *et al.* (1930) who followed up cases operated on by Royle in England concluded: (1) "The operation of ramisection as performed by Royle is without effect upon the rigidity of extrapyramidal tract disease." (2) Cases of hemiplegia and quadriplegia in children may be temporarily benefited. The diminution of tone and improvement of function, however, are short lived. (3) "The operation therefore appears to have no place of value in the treatments of spastic weakness." Herz (1930) who observed 33 cases in which Royle carried out sympathectomy in the treatment of various spastic conditions in Australia, reported that the beneficial results obtained in these cases are negligible.

Later reports of the results of sympathectomy in the treatment of spastic paralysis, of which there have been few, are less optimistic than the earlier ones. In most instances the benefits derived, which probably were due mainly to increased cutaneous circulation and altered muscle metabolism, have not been regarded as sufficient to warrant such a drastic procedure.

Bronchial Asthma.—According to current teaching, based on adequate physiological data, stimulation of the sympathetic pulmonary nerves

commonly results in inhibition of the bronchial musculature and stimulation of the parasympathetic nerves commonly results in bronchoconstriction Constriction of the bronchial vascular bed also is mediated through the sympathetic nerves (see Chapter IX) Sympathectomy in the treatment of bronchial asthma, therefore, is physiologically unfounded. A survey of the literature nevertheless shows that this form of treatment has been applied in many cases In the hands of certain surgeons, according to their published reports, both unilateral and bilateral cervical sympathectomy resulted in benefit to the patient in a high percentage of cases. Others reported only failures. The early reports of Kummell (1923–1926) were sufficiently optimistic to inspire widespread interest in this form of treatment. Although he recognized that the bronchoconstrictor fibers are mainly parasympathetic, he assumed that cervical sympathectomy results in interruption of a sufficient number of bronchoconstrictor fibers to account for diminished bronchial spasm in asthmatic patients.

In experiments reported by Braeucker and Kummell, Jr (1925), bronchial spasms simulating asthmatic attacks in man were induced in animals (rabbit, ape) by stimulating the medulla oblongata, vagus or sympathetic nerves and by certain other procedures These spasms did not occur following section of the bronchial rami of the vagus nerves, consequently, it may be assumed that bronchial spasm induced by sympathetic stimulation may be due to reflex vagus excitation due to stimulation of the visceral afferent spinal nerve components associated with the sympathetic nerves supplying the bronchi. It seems not improbable, therefore, that the cessation of asthmatic attacks observed in certain cases following cervical sympathectomy may have resulted from interruption of the afferent conduction pathways from the bronchial mucosa to the spinal cord, thus preventing reflex stimulation of the vagus center The bilateral effect of unilateral cervical sympathectomy, reported in certain cases, could be explained on the assumption that the distribution of visceral afferent, like that of the sympathetic innervation of the bronchi, is not strictly unilateral, but some fibers cross over to the bronchi on the opposite side

Although there is no rational physiologic basis for sympathectomy in the treatment of bronchial asthma, and in spite of the high percentage of failures reported, this method of treatment has not been entirely abandoned In reporting the late results of stellectomy in the treatment of bronchial asthma, Leriche and Fontaine (1938, 1939) cited certain cases in which beneficial results of bilateral stellectomy have lasted for several years They still regard this procedure as the treatment of choice as a last resort in severe cases of bronchial asthma

Encouraging results of paravertebral injections of procaine and alcohol in the treatment of bronchial asthma have been reported particularly by Stern and Spivak (1930), Du Bose (1931) and Levin (1934). Beneficial results of this form of treatment can be explained with less difficulty than beneficial results of sympathectomy, since the infiltrating chemical substances undoubtedly block some of the pulmonary branches of the vagi as well as the sympathetic nerves Levin (1934) advocated nerve blocking by paravertebral injection particularly in cases of intractable asthma of long standing.

From the physiological point of view, surgical intervention involving the parasympathetic pulmonary nerves in the treatment of bronchial

asthma appears to be more rational than sympathectomy. Phillips and Scott (1929) first reported surgical treatment of this kind. Rienhoff and Gay (1938) reported bilateral resection of the posterior pulmonary plexus in 10 severe cases. Of these patients, 4 remained free of attacks two years after operation and had returned to work, 4 others suffered occasional mild attacks all of which could be controlled by medical treatment, only 1 showed no improvement. These results are impressive but either resection of the pulmonary branches of the vagi or the posterior pulmonary plexuses must be regarded as a drastic operative procedure.

Gastro intestinal Disorders.—**Cardiospasm.**—The response of the cardiac sphincter to either sympathetic or parasympathetic stimulation is conditioned by the tonic state of the muscle (see p. 233). The effect of either nerve stimulation or partial denervation, consequently, cannot be predicted with certainty in any given case, except as indicated by diagnostic tests. Since both the vagus and the sympathetic nerves may mediate either excitation or inhibition of the sphincter muscle, there is no reason to assume that cardiospasm can be abolished by interruption of either the vagus or the sympathetic nerves supplying this muscle.

Knight and Adamson (1935) reported the results of surgical intervention involving resection of the left gastric artery and vein with the plexus of nerves associated with these vessels in the treatment of 5 cases of achalasia of the esophagus with cardiospasm. This procedure undoubtedly interrupts the major portion of the sympathetic and some portion of the vagus fibers to the cardiac sphincter. In one patient the operation resulted in complete relief, another showed marked improvement. The other three showed signs of recurrence. Craig, Moersch and Vinson (1934) carried out bilateral cervicothoracic sympathectomy with good immediate results in cases in which preoperative nerve blocking with procaine afforded temporary relief. In other reported cases in which bilateral sympathectomy was carried out the results have been unimpressive. The results of surgical intervention directed toward the vagus nerves also have been disappointing (Ochsner and de Bakey, 1940).

In the selection of cases of achalasia and cardiospasm for surgical treatment directed toward the innervation of the cardia, it is important to differentiate between true cardiospasm and hypertrophic stenosis of the cardia. Certain cases in the former category undoubtedly may be benefited by nerve section, particularly if preoperative nerve blocking affords temporary relief. Beneficial results of nerve section in cases in the latter category are not to be expected.

Gastric Acidity.—Gastric acidity not uncommonly is associated with parasympathetic hypertonus. On the basis of this clinical observation and the fact that the parasympathetic innervation of the stomach plays a major rôle in the regulation of gastric secretion, interruption of the vagus branches to the stomach may be expected to result in reduced gastric acidity. Pieri and Lanferno (1930), who cut the vagus nerves either above or below the diaphragm in 8 patients, found gastric acidity reduced following operation but in the course of a few months the acid values returned to normal. These results are in full accord with the experimental findings of Hartzell (1929) that total vagus section above the diaphragm in dogs resulted in marked reduction in free and combined acid in the stomach and those of Vanzant (1931) that the gastric acid values were restored to the

preoperative level two years after vagus section, although the vagi had not reestablished functional connections in the stomach. In 6 clinical cases reported by Weinstein *et al* (1944), incomplete vagotomy exerted no significant influence on the nervous phase of gastric secretion. On the basis of their experience, they concluded that gastric vagotomy alone is not to be recommended as a therapeutic procedure.

Congenital Megacolon (Hirschsprung's Disease).—Hurst (1919) advanced the theory that the underlying cause of congenital megacolon is an achalasia of the pelvi-rectal (O'Beirne's) sphincter or the internal sphincter ani. According to this theory, peristaltic waves passing down the descending colon, which should evacuate the bowel, are arrested at one or the other of these sphincters due to its inability to relax, resulting in distention and hypertrophy Fraser (1926) also regarded failure of one or the other of these sphincters to relax as a primary condition of congenital megacolon and advanced the opinion that this failure is due to a delay in the acquisition of the power of inhibition Rankin and Learmonth (1933) recognized dysfunction of the sympathetic innervation of the large intestine as a major factor in the etiology of congenital megacolon but expressed the opinion that this condition is the result of a mixed pathogenesis.

The data on which the assumption that in congenital megacolon the influence of the sympathetic nerves on the large intestine exceeds that of the parasympathetic nerves is based appear to be conclusive Relief of chronic constipation, furthermore, has been observed repeatedly as a result of lumbar sympathectomy carried out in the treatment of various other syndromes. In view of these facts, sympathetic denervation of the large intestine may be regarded as a rational procedure in the treatment of congenital megacolon Complete or partial relief of this condition, particularly in young children, has been reported by various investigators, including Wade and Royle (1927), Judd and Adson (1928), Wade (1930), Barrington-Ward (1932), Adson (1937), Leriche (1937) and others In order to avoid sympathetic denervation of the lower extremities, Rankin and Learmouth (1930, 1932) resected the inferior mesenteric plexus and the upper portions of the hypogastric plexuses, with essentially the same effects on congenital megacolon as those of lumbar sympathectomy. Gibbens (1932) reported satisfactory results of resection of the inferior mesenteric plexus alone.

The most satisfactory results of sympathetic denervation in the treatment of congenital megacolon have been obtained in young children before hypertrophy of the distended colon had become excessive. Satisfactory results have been reported in older children and adolescents in some cases. The value of this form of therapy in the treatment of megacolon and the advantage of its early application may be regarded as adequately demonstrated

Preoperative nerve blocking by paravertebral injection of procaine may be useful in the selection of cases suitable for operation Scott and Morton (1930) have shown that megacolon of neurogenic origin can be differentiated from other types by observing the effect of spinal anesthesia on the motility of the colon. Scott (1936) advocated repeated lumbar subarachnoid injections of procaine as a therapeutic measure in certain cases Telford and Simmons (1939) reported restoration of normal bowel function in young children in certain cases by repeated spinal anesthesia. Law

(1940) reported encouraging results obtained by administration of acetyl beta methylcholine bromide accompanied by auxiliary aids such as liquid petrolatum and an occasional enema until the evacuation habit is established. If adequate evacuation of the bowel can be effected by these measures, the patient obviously should not be subjected to surgical intervention. On the other hand, if these measures afford only temporary relief, the measure of such temporary relief may be regarded as an indication of the relief to be expected from sympathetic denervation.

Visceral Pain.—The afferent innervation of the thoracic and abdominal viscera includes both vagus and spinal nerve components but only the latter conduct impulses of pain (see Chapter XIX). These pain-conducting fibers reach the viscera via the sympathetic nerves. Those which supply the abdominal viscera reach the abdominal plexuses mainly via the splanchnic nerves. The afferent innervation of the pelvic viscera includes spinal nerve components associated with the thoracolumbar and the sacral preganglionic outflows and some afferent components incorporated in the pudendal nerves. The pain conducting pathways from the pelvic viscera are less clearly demarcated than those from the thoracic and abdominal viscera. Impulses of pain probably are conducted from the more distal pelvic viscera via both the hypogastric and the pelvic nerves. Whenever pelvic disease extends to parietal structures the pudendal nerves also play a prominent role in pain conduction.

Pain in Pulmonary Disease.—Nerve blocking by means of paravertebral injections of alcohol has been carried out for the relief of intractable pain due to pleural irritation in pulmonary tuberculosis and other diseases (Swetlow, 1926) without marked success. Blocking of the sympathetic nerves with the afferent fibers associated with them obviously is inadequate to relieve this pain due to the fact that conduction from the parietal pleura involves somatic afferent nerve components. The lung and the visceral pleura are highly insensitive. Pain due to pulmonary disease therefore does not become severe unless the parietal pleura becomes involved in the disease process giving rise to painful stimulation of somatic afferent components of the intercostal nerves. These fibers may be blocked temporarily by paravertebral alcohol injections but usually recover the capacity to conduct in a relatively short time.

Pain from the Gastro-intestinal Tract.—Since the pain-conducting fibers from the gastro-intestinal tract traverse the sympathetic nerves they can be interrupted by sympathetic or splanchnic nerve section. The appropriate level for surgical intervention may be determined by diagnostic nerve blocking. Fibers which conduct impulses of pain from the esophagus are associated with many sympathetic rami. Most of those from the lower thoracic portion of the esophagus traverse the fifth and sixth thoracic segments of the sympathetic trunk. Extirpation or chemical blocking of these segments, therefore, may be expected to relieve pain due to disease of the lower portion of the esophagus. Impulses of pain from the stomach enter the spinal cord in the seventh and eighth thoracic segments (Läwen, 1923). Extirpation or blocking of these segments of the sympathetic trunks may be expected to abolish true gastric pain. Severe gastric pain of long duration, however, occurs only rarely unless the disease extends into the mesenteries and to the dorsal abdominal wall, when somatic pain receptors are stimulated. The results of nerve blocking or sympathetic

ganglionectomy for the relief of intractable gastric pain have not been impressive, probably due to the involvement of somatic afferent fibers in most of the cases which have been subjected to this method of treatment.

Chronic intractable pain due to stimulation arising in the intestine alone occurs only rarely. The segments in which the afferent fibers stimulated in such cases traverse the sympathetic trunks can be determined by diagnostic nerve blocking. Permanent blocking or extirpation of these segments bilaterally may be expected to abolish the pain. Pain due to malignant disease of the intestinal tract is rarely amenable to this form of treatment since the discomfort usually is due either to obstruction or involvement of the mesentery and somatic nerves.

Pain from the Biliary System.—Impulses of pain arising in the gall bladder are conducted centralward through the right major splanchnic nerve (Davis, Pollock and Stone, 1932). Most of the impulses of pain from the entire biliary system are conducted through this nerve. The left splanchnic nerve conveys relatively few pain-conducting fibers from this system (Moore and Singleton, 1933) Resection of the right major splanchnic nerve or resection of both the major and minor splanchnics, consequently, may be expected to abolish pain of biliary origin in most cases The effectiveness of this method of treatment in patients with chronic biliary pain has been amply demonstrated (Craig, 1934; White and Smithwick, 1941).

Abdominal Pains of Obscure Origin.—Abdominal pains, the causative factor of which could not be determined even by exploratory laparotomy, have been relieved in certain cases by sympathetic ganglionectomy or ramisection (Archibald, 1928; Alvarez, 1931). Scrimger (1934) reported 2 cases of this kind with well-defined referred somatic hyperalgesia in which both the visceral pain and the referred phenomena were relieved by sympathectomy in the segments indicated by paravertebral nerve blocking used as a diagnostic test. In cases of obscure abdominal pain with referred phenomena, the latter may indicate the appropriate segments for surgical intervention. In the absence of referred phenomena, nerve blocking by paravertebral injections of procaine affords a useful aid in determining the segmental level of the pain-conducting pathways involved.

Pain of Renal Origin.—In view of the anatomical arrangement of the innervation of the kidney, resection of the renal plexus or the splanchnic nerves may be expected to abolish pain of renal origin Hess (1930) reported 10 cases of renal pain due to kinked ureters, small nephroses and movable or ptosed kidneys in which the renal plexus was resected. Nephrectomy was avoided in all these cases and in 6 cases the relief obtained was regarded as complete. Distention of the renal pelvis during pyelography was no longer painful and nausea and vomiting were eliminated. Wharton and Hughson (1931) and Hepburn (1934) reported relief of intractable pain of ureteral origin following sympathetic denervation

Pain from the Urinary Bladder.—Data bearing on the anatomic arrangement of the pain-conducting pathways from the bladder are not in full agreement. Afferent nerve fibers associated with the sympathetic innervation of the bladder traverse the hypogastric plexus. Afferent nerve fibers also reach the bladder via the pelvic and pudendal nerves. Munro (1937) could detect no diminution in sensation following resection of the superior hypogastric plexus either on distending the bladder or on the

application of tactile or thermal stimuli in the course of cystoscopy. Langworthy, Kolb and Lewis (1940) have recognized evidence of vague sensations due to filling of the bladder in cases of sacral nerve paralysis but regard the conduction of actual pain impulses from the bladder via the hypogastric nerves as highly improbable. Conduction of impulses of pain from the bladder via the pelvic nerves appears to be amply demonstrated.

In spite of the data cited above, resection of the hypogastric plexuses has been carried out for the relief of pain of vesical origin in many cases. Favorable results of this operation have been reported by Pieri (1926), Vrnmay (1927), Learmonth and Braasch (1933), Scott and Schroeder (1938) and others. Nesbit and McLellan (1939) have advanced the opinion that resection of the hypogastric plexus may relieve bladder pain of certain types not by interrupting pain conducting pathways but by reducing spasm of the internal vesical sphincter. They reported a series of patients suffering from dysuria associated with various forms of chronic cystitis with marked vesical spasm in whom the results of resection of the superior hypogastric plexus were uniformly good. White and Smithwick (1941) regard this operation as of limited value in the treatment of intractable cystitis.

The results of resection of the hypogastric plexuses for the relief of pain due to malignant disease of the bladder have not been encouraging. Rocher (1921) and Learmonth (1931) reported relief of pain in such cases following resection of the ganglia at the base of the bladder, thus effecting complete vesical denervation. This operation may be expected to abolish vesical pain except in cases in which the disease has extended too far into the perivesical area, but it is a drastic procedure which results in complete paralysis of the bladder, thus necessitating catheterization.

Pain from Internal Genital Organs.—The nerve fibers which conduct impulses of pain from the internal genital organs except the gonads reach the pelvis mainly through the hypogastric plexuses. Interruption of these plexuses therefore may be expected to abolish pain arising in these organs. The relief of pain in dysmenorrhea and other uterine conditions following resection of the hypogastric plexuses has been most striking. Favorable results of this operation in cases of dysmenorrhea have been reported by various investigators, including Fontaine and Herrmann (1932), Wetherell (1933), Adson and Masson (1934), Pemberton (1935), Counsellor and Craig (1935), Cotte (1937), Marshall and Poppen (1937), Meigs (1939), Colcock (1941) and others. It is not followed by bowel or vesical complications and does not interfere with subsequent pregnancy.

Resection of the hypogastric plexuses for the relief of pain in malignant disease of the uterus has been less successful, although encouraging results of this operation have been reported (Fontaine and Herrmann, 1932; Wetherell, 1933; Greenhill and Schmitz, 1933; Adson and Masson, 1934). According to White and Smithwick (1941), malignancy of the uterus usually does not give rise to intense pain until the disease has extended into the parametrial and paracervical tissues. In the latter case impulses of pain are conducted through the lower sacral nerves. After the disease has extended into the pelvic wall, pain conduction through somatic nerves is more pronounced than through the visceral nerves.

Painful Disorders of the Extremities.—Disorders of the extremities such as causalgia, cryalgesia, traumatic arthritis and amputation stump neu-

ralgia which are characterized by intractable pain not infrequently are associated with circulatory and sudomotor disturbances and trophic changes manifested by edema, glossy skin, muscular weakness and atrophy of the bone These complications not infrequently follow relatively minor injuries to nerves, blood vessels or ligaments The degree of disability caused by them and the difficulty of treatment frequently are disproportionate to the apparent minor significance of the primary injury. The causative factors in these conditions are not well known. The vasomotor changes undoubtedly play a significant rôle. Most frequently there is hyperemia in the acute stage, followed by cyanosis, coolness and excessive perspiration in the chronic stage. These phenomena emphasize the extent of sympathetic dysfunction and suggest that the trophic and other manifestations, including the pain may be aggravated by the excessive sympathetic reflex activity This hypothesis, furthermore, is supported by the fact that interruption of the sympathetic pathways by surgical intervention or by chemical nerve blocking has in many instances resulted in alleviation of the pain and improvement in associated symptoms

Causalgia —As defined by Mitchell, Morehouse and Keen (1864), who first described this condition in soldiers following penetrating wounds, causalgia is characterized by hyperalgesia of the hand or foot following an injury in the region of a peripheral nerve. The sensory phenomena vary in intensity from a trivial burning sensation to excruciating pain. The pain is constant and exacerbations are brought on by the slightest physical or emotional stimuli. The skin in the affected area may become dry and scaly, but more frequently it is cold and moist Trophic changes of the skin are not uncommon.

De Takats (1943) has pointed out that painful vasodilatation accompanied by spreading neuralgia is a major factor in the causalgic state in many cases As indicated by the results of plethysmographic studies (Miller and de Takats, 1942), the flow of blood in the injured limb is persistently increased. Heat increases it still further in excess of the flow in the uninjured limb, whereas cold reduces the flow in a lesser degree in the injured limb than in the uninjured one The painful, throbbing character of this chronic vasodilatation, which is abolished by sympathetic nerve block or by arterial compression and aggravated by venous stasis, indicates capillary hypertension, consequently, any treatment which results in reduction of capillary pressure and capillary dilatation should be beneficial

De Takats has emphasized the advantage of early treatment in these cases In his experience early, mild cases have responded satisfactorily to immobilization and daily injections of a 1 per cent solution of procaine hydrochloride in the injured area After the neuralgia has spread beyond the site of the injury he advises paravertebral injections of procaine, repeated as the pain reappears, or sympathetic ganglionectomy In the later stages of the disease, many cases fail to respond to treatment of this kind If nerve blocking by paravertebral injections of procaine fails to relieve the symptoms temporarily, according to de Takats, sympathectomy will also fail

Relief of causalgic pain in the upper extremity following cervicothoracic sympathectomy had previously been reported, particularly by Spurling (1935), Kwan (1935) and Homans (1940). Homans also reported a case in which resection of the occluded radial artery was followed by relief of

causalgic pain and improvement in the associated symptoms. Relief of causalgic pain in the foot following crushing of the peripheral nerves has been reported by White (1945) and others.

Since advanced causalgic disease in many instances is not amenable to treatment either by sympathectomy or nerve crushing, the selection of cases for such treatment is important. Those suitable for sympathectomy or nerve crushing can be readily differentiated from those which are not by diagnostic nerve blocking with procaine.

Cryalgesia.—Data bearing on the treatment of injury due to cold by sympathectomy as yet are meager. In view of the nature of such injury, no material benefit of sympathectomy should be expected in its early phases. On the basis of a histological study of the damaged tissues in cases of immersion foot, White and Warren (1944) advanced the opinion that the pain associated with the early phase of the inflammation is due to anoxemia of the injured superficial tissues and nerve endings, while the aching and burning pain which persists following the inflammatory phase is due to contraction of the newly formed interstitial connective tissue and collagen which affects blood vessels, muscle fibers and nerves. Pain of this type, according to their observations, tends to clear when the collagen surrounding the nerves ceases to contract, which may require six to eight months.

Telford (1943) reported five cases in which the late results of injury from cold were treated by preganglionic sympathectomy with benefit to the patient in every case. In four of these patients the injury was due to frostbite. The fifth was a seaman with immersion foot who was unable to walk eight months after the injury and complained of constant burning pain in the feet which were tender and showed excessive sweating and ulceration of the toes. Bilateral lumbar sympathectomy resulted in immediate relief of the pain and rapid healing of the ulcers.

Amputation Stump Neuralgia.—Alleviation or relief of amputation stump pain following sympathetic ganglionectomy (Flothow, 1930; Spurling, 1930; White and Smithwick, 1941) and by chemical nerve blocking by means of paravertebral injections (Livingston, 1938) have been reported. In many cases amputation stump pain is not amenable to treatment of this kind. In the selection of cases for treatment by sympathectomy or permanent nerve blocking, therefore, it is important to determine by diagnostic nerve blocking with procaine whether temporary abolition of the pain can be effected by functional interruption of the sympathetic rami.

Pain in Paralyzed Extremities.—The major pain-conducting pathways from the extremities are well known. In certain cases, as has been pointed out by White and Smithwick (1941), interruption of all the known sensory nerves has been followed by continued pain in an otherwise insensitive area. They also pointed out that in numerous cases section of the posterior roots of the brachial plexus from C III to T II has failed to relieve major amputation stump neuralgia in the upper extremity. Slaughter (1938) reported severe burning, pricking pains in the legs of a man thirty-one years of age following complete transection of the spinal cord at the level of the first lumbar vertebra which subsided following bilateral extirpation of the lumbar segments of the sympathetic trunk and section of the hypogastric nerves. Hyndman and Wolkin (1941) reported 2 cases in which annoying sensory phenomena in the legs and feet following complete

paralysis of both lower extremities caused by fracture of the second lumbar vertebra, subsided following bilateral lumbar sympathectomy The extremities of these patients were completely anesthetic to all tests for exteroceptive and proprioceptive sensibility up to the middle level of the thigh Patency of the sympathetic innervation of the lower extremities was demonstrated by thermoregulatory and sweating tests. In an attempt to explain the sensory phenomena observed in the anesthetic extremities of these patients, Hindman and Wolkin postulated the existence of afferent sympathetic fibers or antidromic conduction in efferent sympathetic fibers.

Kuntz and Farnsworth (1931) demonstrated nerve fibers of spinal ganglion origin in the gray communicating rami which join the nerves which supply the upper and lower extremities These fibers are afferent components of the spinal nerves through the ventral roots of which the preganglionic fibers involved in the sympathetic innervation of the extremities reach the sympathetic trunk ganglia Those which traverse the gray communicating rami which join the nerves to the upper extremity are components of the upper thoracic nerves. probably including the first to the fifth or sixth Those which traverse the gray communicating rami which join the nerves to the lower extremity are components of the lower thoracic and the first and second lumbar nerves. Afferent conduction from the extremities into the spinal cord through components of spinal nerves other than those through which the extremities receive their voluntary innervation, which traverse the sympathetic trunks and communicating rami also has been demonstrated in experimental animals (Kuntz and Saccomanno, 1942).

In view of these anatomical and experimental data the sensory phenomena in the paralyzed, insensitive extremities of the patients referred to above can be explained most satisfactorily on the assumption that the afferent impulses are conducted into the spinal cord through afferent spinal nerve components which traverse the sympathetic trunk and communicating rami On the same assumption, cervicothoracic sympathectomy combined with section of the posterior roots of the brachial plexus would be a more rational procedure for the relief of amputation stump neuralgia in the upper extremity than either posterior root section or sympathectomy alone

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The principal reference is indicated by **bold-face type.**

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